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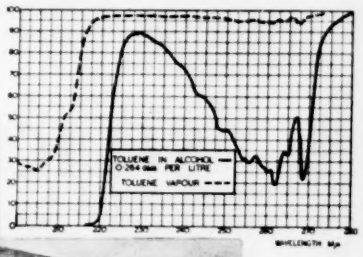

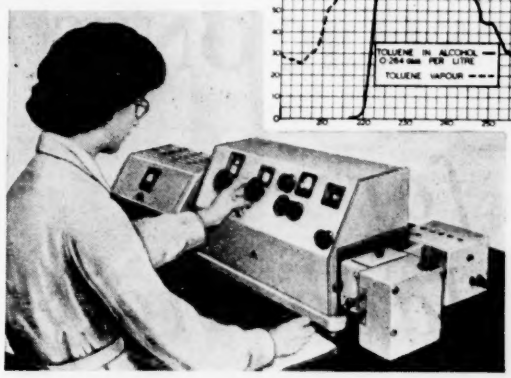

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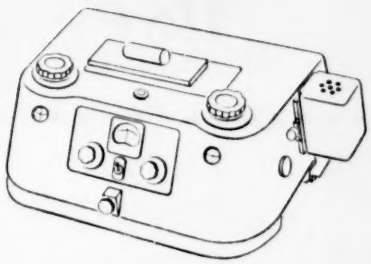

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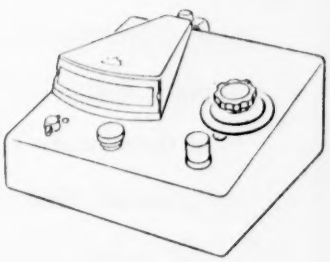

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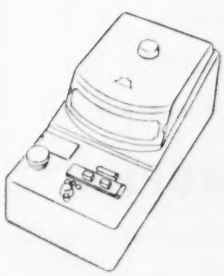

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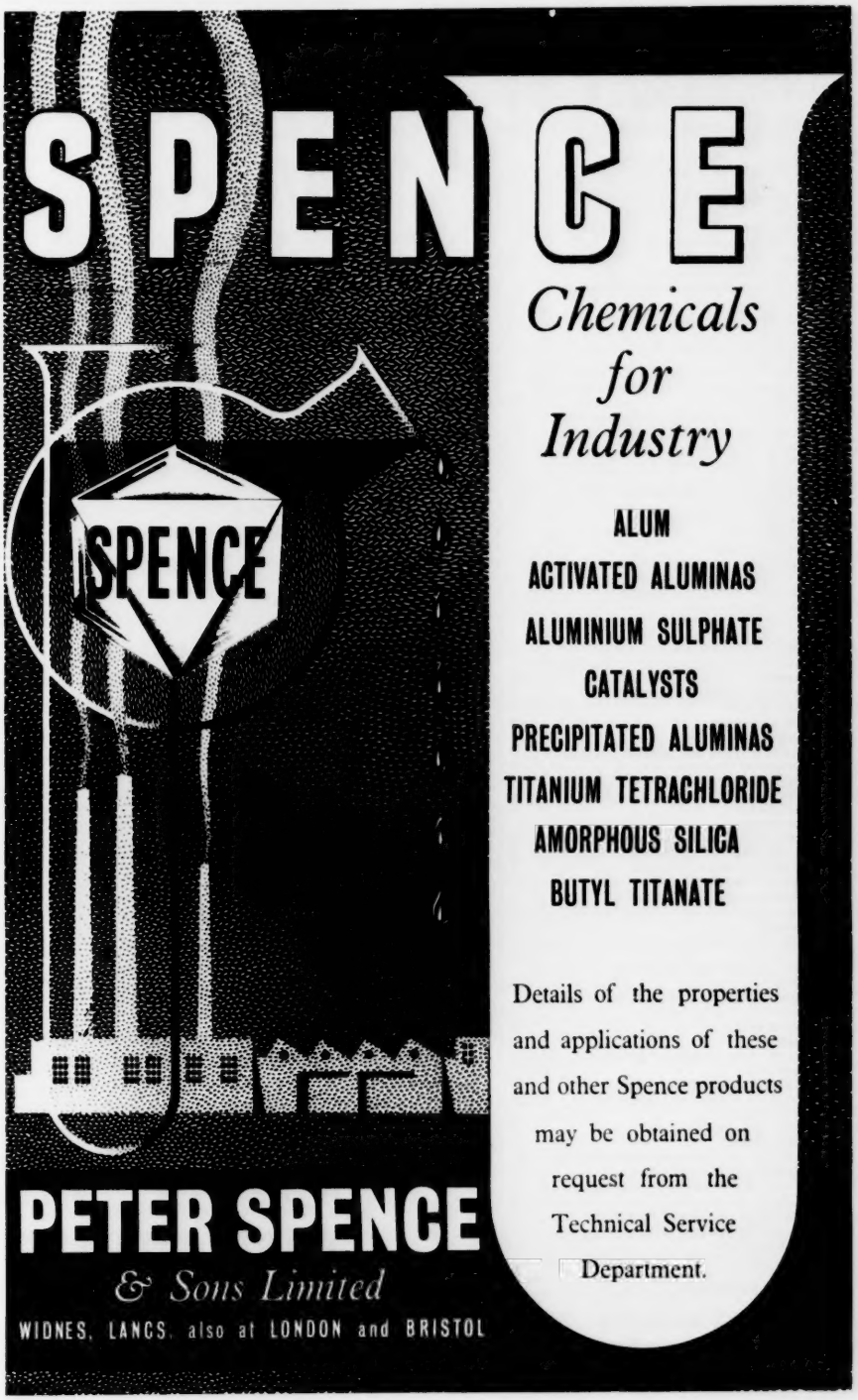
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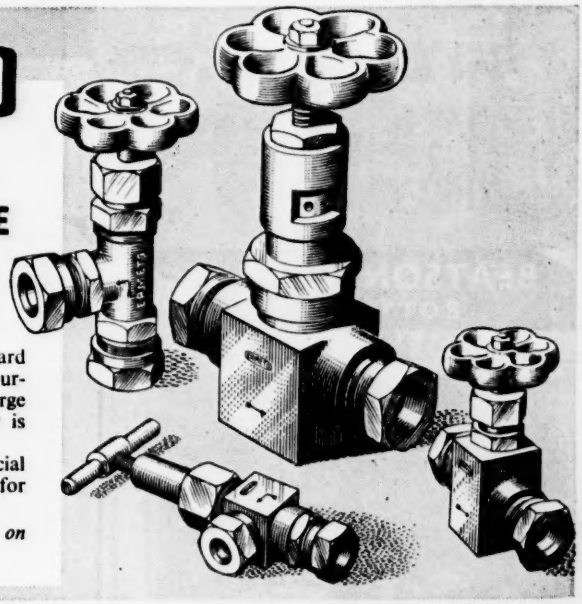

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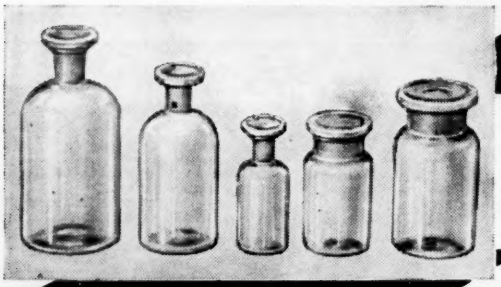

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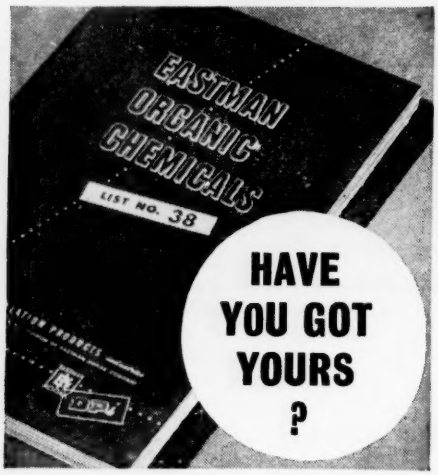

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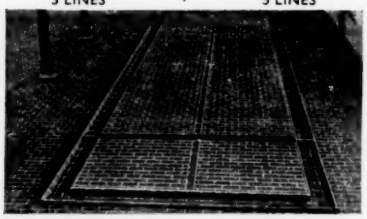

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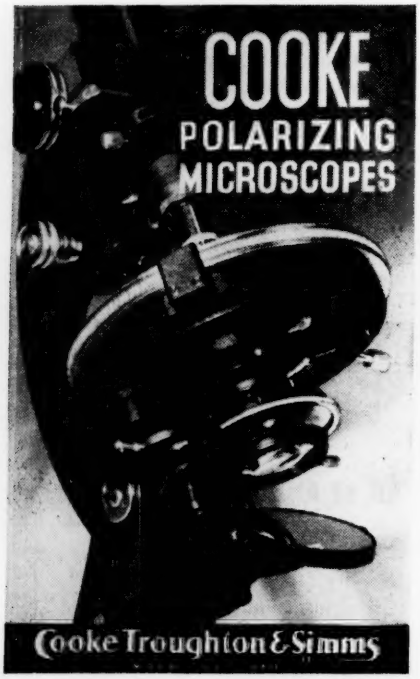

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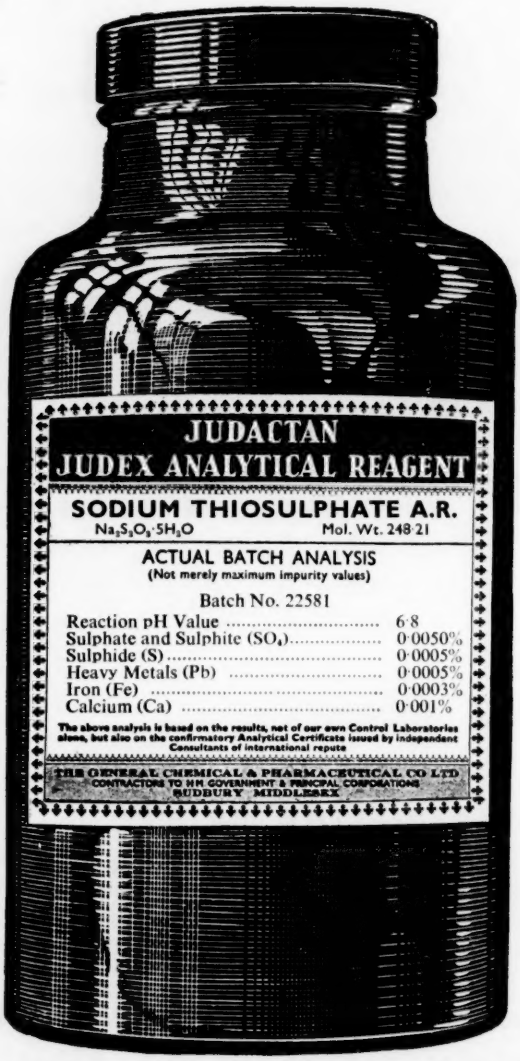
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339. *The Polymerisation of Styrene by Titanic Chloride. Part I. Kinetics.*

By P. H. Plesch.

The polymerisation of styrene by titanic chloride in hexane, toluene, and various alkyl halides was investigated by an adiabatic technique. In the absence of deliberately added co-catalyst the reaction rate in hexane and in toluene could be made very small (zero in two experiments) by rigorous purification of the solvent. This slow reaction is considered to be due to adventitious co-catalyst, probably water. With trichloroacetic acid as co-catalyst the rate in toluene has an activation energy of −1·5 kcal./mole. In ethylene dichloride and dibromide the reaction rate is greatly accelerated by water. In the absence of water the rate in the former solvent is proportional to the catalyst concentration and the square of the monomer concentration. The activation energy is −8·5 kcal./mole.

The polymerisation of styrene catalysed by metal halides has been studied quantitatively by several groups of workers in recent years (Gwyn Williams, *J.*, 1938, **246**, 1046; 1940, 775; 1948, 1867; Pepper, *Nature*, 1946, **158**, 789; *Trans. Faraday Soc.*, 1949, **45**, 397; Medvedev and Gantmakher, *Zhur. Fiz. Khim.*, 1949, **23**, 516; *Chem. Abs.*, 1949, **43**, 7295; George, Mark, and Wechsler, *J. Amer. Chem. Soc.*, 1950, **72**, 3891, 3896; Jordan and Mathieson, *Nature*, 1951, **167**, 523; *J.*, 1952, 611, 621). These and related researches have been summarised and discussed in "Cationic Polymerisation and Related Complexes" (ed. P. H. Plesch, Heffer and Son, Ltd., Cambridge, 1953).

The present investigation was undertaken to discover whether the polymerisation of styrene by titanic chloride, like that of *iso*butene, requires a co-catalyst, to find a suitable solvent for detailed investigations, and to obtain some more information on the chemistry and kinetics of this reaction.

Experimental

Apparatus.—The reaction vessel and its fittings are shown in Fig. 1. It was a flanged, double-walled vessel connected to a high-vacuum system so that the space between the walls could be evacuated at will. The flanged vessel-head carried a mercury-seal stirrer and four B. 14 sockets for admission of solvent, catalyst solution, and monomer and serving as inlets and outlets for dry nitrogen, the fourth socket carrying a thermometer. The flange and all joints and taps were lubricated with silicone grease.

The reaction vessel was connected to the solvent and catalyst reservoirs and burettes and to the dry nitrogen supply. All ducts opening to the atmosphere were protected from ingress of moisture by glass spirals embedded in carbon dioxide–ethanol.

Procedure.—The reaction vessel was swept out for about 2 hr. with dry nitrogen boiling off liquid nitrogen. After this the solvent was run in, either from a reservoir attached to the apparatus, *via* a burette, or by pipette (technique "A"). In later experiments it was distilled directly into the reaction vessel from an all-glass still, in an atmosphere of dry nitrogen, the quantity being gauged to the nearest 1 c.c. from graduations on the reaction vessel (technique "B"). When temperature equilibrium had been reached, the Dewar space of the reaction vessel being evacuated to a pressure of $<10^{-3}$ mm. Hg, the catalyst solution was run in from the reservoir *via* a burette. When an alkyl halide was used as solvent, the reaction was started by pipetting the monomer rapidly into the solvent–catalyst solution. When a hydrocarbon was used as solvent, the catalyst, co-catalyst, and monomer were usually added in this order, but, when it was desired to test whether an appreciable quantity of adventitious co-catalyst was present, the monomer was added after the catalyst, and after that, if necessary, the co-catalyst. Temperature readings on a mercury or pentane thermometer reading to 0·1° were taken at regular intervals until the reaction had subsided and the cooling rate was constant. For work at other than room temperatures the reaction vessel was surrounded by a suitable bath. In the later stages of the work it was found useful to add several portions of monomer to a given solution of catalyst, and to observe the polymerisation of each one in succession.

With ethylene dichloride as solvent this technique of repeated monomer addition made it possible to obtain a reasonable degree of reproducibility and to get results more rapidly. The disadvantage of this technique is that the molecular weight of the products of the individual reactions cannot be determined.

When the reactions were over, the reaction mixtures were poured into dilute sodium carbonate solution to hydrolyse the catalyst.

No attempt was made to calibrate the reaction vessels accurately, but from the temperature rises corresponding to 100% polymerisation of various quantities of styrene in 50 c.c. of ethylene dichloride it was found that a rate of 1°/min. was equivalent to an absolute rate of approx. 0·035 mole $l.^{-1}$ $min.^{-1}$ in this solvent. For 50 c.c. of toluene 1°/min. corresponded approx. to 0·032 mole $l.^{-1}$ $min.^{-1}$.

The adiabatic technique is justified because (*a*) there is no *a priori* reason why the rate of temperature rise should not be proportional to the rate of polymerisation provided the chain length is great enough to swamp the effect of the first one or two propagation steps for which the heat of reaction may be different from that of subsequent steps, (*b*) the total temperature rise during polymerisation is linearly related to the initial monomer concentration when

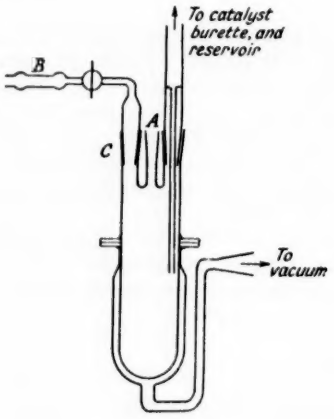

FIG. 1. *The reaction vessel.*

The internal dimensions of the reaction vessel are 5 × 12 cm.

A = Socket for mercury seal stirrer.
B = Calcium chloride tube.

The monomer is added through socket *C*. The sockets carrying the thermometer and the solvent inlet are not shown.

polymerisation is complete, and (*c*) the temperature changes involved and the activation energies are small.

Materials.—Styrene. Styrene (>99% pure, Koppers; 100 c.c.), stabilised with 4-*tert.*-butylcatechol, was shaken with 10% sodium hydroxide solution and twice with water, and left for 48 hr. on solid sodium hydroxide. It was distilled in a high vacuum from potassium hydroxide, and the middle fraction stored in a black bottle over potassium hydroxide powder. Even after several months it gave only a very faint turbidity (polystyrene) when poured into excess of ethanol; it had n_D^{25} 1·544.

Hexane. This was purified, and the titanic chloride solution in hexane prepared, as described previously (Plesch, *J.*, 1950, 543). The concentration of the latter was 0·3M.

Trichloroacetic acid. This was purified and its solution in hexane made up as previously described (*idem, ibid.*).

Toluene. Several specimens of toluene, purified in different ways, were used. Phosphoric oxide was not used for drying as it is appreciably soluble in toluene. Toluene I was purified by nitrous fumes, concentrated sulphuric acid, and dilute sodium hydroxide, distilled, pyrolysed by Szwarc's method (*J. Chem. Phys.*, 1948, **16**, 128), and stored over calcium chloride. For toluene II, Catarex toluene (2½ l.) was refluxed for 1 hr. with aluminium chloride and then distilled through a 60-cm. Vigreux column; about three-quarters distilled over within 0·2° at a reflux ratio of 10 : 1. The distillate was washed with dilute sodium carbonate solution to free it from some aluminium chloride which came over with it. It was dried ($CaCl_2$) and distilled, and the fraction (almost 90%) distilling within 0·1° was collected and stored over calcium chloride. For toluene III, toluene II was refluxed for 1 hr. with 20 g. of sodium, then distilled and stored over fresh sodium chips. Toluene V was prepared from Catarex toluene in the same was as toluene I but, instead of being pyrolysed, it was refluxed with sodium, distilled, and

stored over calcium chloride. Toluene VI was prepared by treating toluene V successively with powdered calcium chloride, powdered soda lime, and phosphoric oxide, and distilling it and storing it over calcium chloride.

Ethylene dichloride. The commercial material (B.D.H.) was purified by shaking it successively with N-potassium hydroxide, water, and solid potassium carbonate. It was distilled from calcium chloride through a well-lagged 60-cm. Vigreux column with a reflux ratio of 5 : 1, and the fraction distilling over a range of 0·3° was collected. The yield was about 70%. If the ethylene dichloride was to be run into the reaction vessel it was stored over calcium chloride, since phosphoric oxide is appreciably soluble in it. If it was to be distilled into the reaction vessel it was stored over phosphoric oxide and later distilled from this.

Ethylene dibromide. The commercial product (Mersey Chemicals; *ca.* 450 c.c.) was treated four times with 98% sulphuric acid (25 c.c.), and washed with water, twice with dilute sodium carbonate solution, and again with water. It was dried ($CaCl_2$) and distilled off phosphoric oxide through a 60-cm. Vigreux column with a reflux ratio of 10 : 1; 350 c.c. distilled within a range of less than 0·1°; n_D^{25} was 1·538. It was stored over calcium chloride in the dark, and distilled off phosphoric oxide into the reaction vessel.

Measurement of Molecular Weight.—The intrinsic viscosities of the polystyrenes were determined viscometrically in toluene solution by the method previously described (Plesch, *loc. cit.*), and from these the mean molecular weights were calculated from the formula $[\eta] = KM^{\alpha}$, with Pepper's constants (*J. Polymer Sci.*, 1951, **7**, 347), *viz.*, $K = 2{\cdot}27 \times 10^{-4}$, $\alpha = 0{\cdot}72$, the concentration being expressed in g. of polymer per 100 c.c. of solvent.

Results

In a search for a suitable solvent, benzene and *cyclo*hexane were discarded because their high f. p.s restrict the temperature range over which the reaction can be investigated, and hexane because the insolubility of the polymer in it may complicate the kinetics; but some useful qualitative information was obtained with the last. Finally, toluene was chosen, and in spite of the extreme difficulty in purifying it, some qualitative results were obtained with it.

Hexane.—In Table 1 are given the initial rates of polymerisation of styrene by titanic chloride in hexane solution without deliberately added co-catalyst, obtained by technique A. The rates are consistently very low. On addition of trichloroacetic acid the polymerisation was greatly accelerated and the ensuing reaction curves (time–temperature) were S-shaped.

TABLE 1. *Rate of polymerisation of styrene in hexane and in toluene without deliberately added co-catalyst.*

Expt. No.	Solvent	Temp.	Concn. of C_8H_8, mole/l.	Concn. of $TiCl_4$, m.mole/l.	Initial reaction rate, °/min.
371	C_6H_{14}	22·5°	0·164	11·3	0
372	,,	21·5	0·164	11·3	0·05
380	,,	22	0·322	11·1	0·1
406	,,	18·5	0·164	5·8	0·02
336	PhMe I	23	0·322	18·5	0·1
365	,, I	−64	0·167	19·2	0
350	,, II	25·5	0·322	18·5	11·6
368	,, III	22°	0·322	18·5	0·7
370	,, III	21·5	0·164	11·3	0·6
373	,, III	22·5	0·164	11·0	0·4
381	,, V	23	0·322	11·1	7
404	,, VI	20·5	0·164	11·3	0·7
405	,, VI	21·5	0·167	5·8	1·5

Toluene.—With technique A it was found that in toluene, however purified, it was not possible to obtain a non-reacting mixture of titanic chloride and styrene, except at low temperatures. The residual reactivity ("blank" reaction) in the absence of deliberately added co-catalyst was very variable from batch to batch of toluene, and also varied slightly during the use of any one batch (Table 1). However, it was found that with toluene I, the slow "blank" reaction could be swamped effectively by using trichloroacetic acid as co-catalyst. The resulting reaction curves showed no acceleration, *i.e.*, the rate decreased monotonically from the initial maximum value. The reaction rate is proportional to a power of the concentration of trichloroacetic acid which is probably unity, but may be as high as 1·3 (Fig. 2). With toluenes II and V the "blank" reaction was very fast and the initial rates of polymerisation

actually diminished with increasing concentration of trichloroacetic acid; but the further treatment of both these samples described above gave toluenes III and V in which the " blank " reaction was much reduced.

In toluene I the activation energy of the initial polymerisation velocity with trichloroacetic acid as co-catalyst was $-1{\cdot}5 \pm 0{\cdot}3$ kcal./mole (Fig. 3).

The molecular weights of the polystyrenes obtained in toluene solution with trichloroacetic acid as co-catalyst were not satisfactorily reproducible. They showed no trend with concentration of co-catalyst, and at a monomer concentration of 0·322 mole/l. and a catalyst concentration of 18 m.mole/l., they lay in the range of 500—800 at 25° and 1000—1200 at −62°.

In contrast to previous experience with *iso*butene (Plesch, *loc. cit.*) it was never found that the polymerisation ceased before all the monomer had been consumed. There is thus no evidence that the co-catalyst is consumed during the reaction. This is supported by the evidence from infra-red spectra presented in Part II (following paper).

FIG. 2.

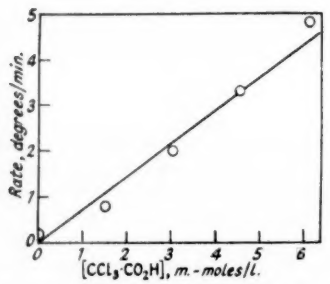

FIG. 3.

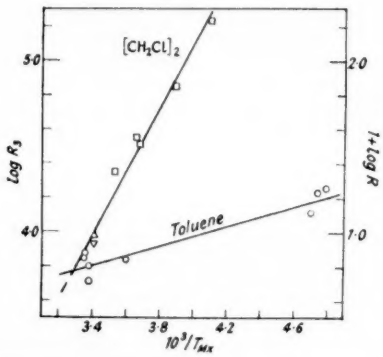

FIG. 2. *The initial rate of polymerisation of styrene by titanic chloride in toluene as a function of the concentration of trichloroacetic acid.*

Temperature 25°. Styrene concn. 0·322 mole/l., titanic chloride concn. 18·5 millimole/l.

FIG. 3. *Variation with temperature of the polymerisation rate of styrene by titanic chloride.*

T_{Mx} is the mean temperature of the interval over which the initial reaction rate was determined.

The left-hand ordinate refers to experiments with $(CH_2Cl)_2$ as solvent (□). Points ▽ and △ are derived from Figs. 5 and 6, respectively, the rest are individual experiments. R_3 is the third-order rate constant in degrees min.$^{-1}$ (mole/l.)$^{-3}$.

The right-hand ordinate refers to experiments with toluene as solvent (○). In these the concentrations were: styrene 0·32 mole/l., $TiCl_4$ 19 m.-mole/l., $CCl_3{\cdot}CO_2H$ 1 m.-mole/l. R is the observed initial rate of polymerisation in degrees/min.

These results make it highly probable that in hydrocarbon solution styrene is not polymerised by titanic chloride alone, but that a co-catalyst is necessary. This would be in agreement with Clark's results (Plesch, *op. cit.*, p. 99) obtained with the system styrene–boron fluoride–carbon tetrachloride.

Alkyl Halides as Solvents.—There is evidence to show that under the influence of catalytically active metal halides, alkyl halides can form positive ions (*e.g.*, Fairbrother, *J.*, 1941, 253), and Pepper (*Trans. Faraday Soc.*, 1949, **45**, 397) has suggested that when styrene is polymerised in ethylene dichloride by stannic chloride the solvent acts as the co-catalyst. Ethylene dichloride, used by Pepper (*loc. cit.*), proved to be a very suitable solvent.

It was found impossible to obtain reproducible polymerisation rates as long as ethylene dichloride dried over calcium chloride was added by technique A; the reaction rate was excessively sensitive to traces of moisture, and when several portions of monomer were polymerised in the same solution, the rate of each successive polymerisation was less than that of the preceding one. When the solvent was distilled off phosphoric oxide directly into the reaction vessel (technique B), and the method of successive monomer additions used, the polymerisation rates were reasonably reproducible. It was found that up to 4 or 5 portions of 0·4 or 0·5 c.c. of styrene could be polymerised in the same batch of 40 or 50 c.c. of ethylene dichloride containing the titanic chloride, without any significant drift in the initial rates of the successive

polymerisations. This is illustrated in Fig. 4 and Table 2. The reaction mixtures were clear and pale yellow. The reaction goes virtually to completion. The yield was determined in several experiments by weighing the polymer contained in 5 c.c. of reaction mixture. In two typical experiments yields of 96% and 100·6% were found. The initial reaction rate was approximately proportional to the first power of the concentration of titanic chloride (Fig. 5) and depended on the square of the initial monomer concentration (Fig. 6). Therefore $-dm/dt = R_3[TiCl_4][Styrene]^2$. The quantities R_s and R_t plotted in Figs. 5 and 6 are given by $R_s = R_3[TiCl_4]$, with [Styrene] = 1 mole/l., and $R_t = R_3[Styrene]^2$, with $[TiCl_4]$ = 1 mole/l. The

TABLE 2. *Polymerisation of styrene in ethylene dichloride by titanic chloride.*

Expt. No.[a]	T_{Mx}[b]	Concn. of $TiCl_4$,[c] m.mole/l.	Initial concn. of C_8H_8, mole/l.	R_s,[d] degrees min.$^{-1}$	R_3,[e] degrees min.$^{-1}$ (mole/l.)$^{-3}$ × 10^{-3}
412. I	21°	10·0	0·104	0·73	6·8
412. II	23	9·9	0·102	0·82	7·9
412. III	24	9·8	0·101	0·95	9·5
413. I	21	5·8	0·106	0·4	5·4
413. II	23	5·7	0·144	1·2	10·0
413. III	24·5	5·6	0·181	1·5	8·2
413. IV	22	5·6	0·0605	0·25	12·2

[a] The Roman numerals indicate successive reactions carried out in the same batch of solvent–catalyst solution. [b] T_{Mx} is the mean temperature of the interval over which the initial reaction rate was determined. [c] This diminishes owing to the increase in volume of the reaction mixture due to the addition of successive portions of styrene. [d] Observed initial reaction rate, corrected for cooling. [e] Third-order rate constant, derived from the relation: Rate ∝ [Catalyst][Monomer]^2.

FIG. 4.

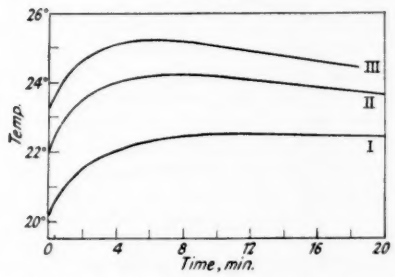

FIG. 5.

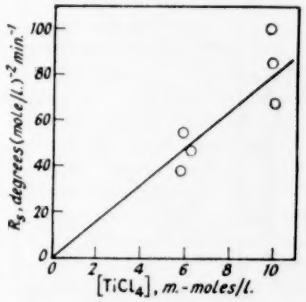

FIG. 4. *Expt.* 412. *Typical time–temperature curves for the polymerisation of successive portions of styrene (I, II, and III) in the same solution of titanic chloride in ethylene dichloride.*
Concentrations as in Table 2.
In each run the styrene was added to the catalyst solution at time $t = 0$.

FIG. 5. *Dependence of the second-order rate constant R_s of the polymerisation of styrene in ethylene dichloride, on the concentration of titanic chloride, at 20°.*

temperature dependence of the third-order rate constant R_3 in degrees (mole/l.)$^{-3}$ min.$^{-1}$ is shown in Fig. 3. The overall activation energy is $-8·5 \pm 1·5$ kcal./mole. The third-order rate constant at 25° is of the order of 10^3 mole^{-2} l.^{2} min.$^{-1}$, which leads to an A factor of about 10^{-3} in the same units.

The effect of water on the reaction rate was studied qualitatively by starting a reaction in the usual way by adding a portion of monomer to the catalyst–solvent mixture, and then, after following the reaction for some minutes, adding 2 c.c. of ethylene dichloride saturated with water (water content approximately 0·2 millimole). The reaction mixture became slightly turbid and its yellow colour deepened markedly. The actual reaction rate increased immediately by a factor of about 40 (reaction 417, IA, Table 3). After this reaction had subsided, further portions of styrene were added. The initial rates of successive reactions diminished steadily, but the rate of the last reaction was still about 4 times greater than that to be expected in the absence of deliberately added water. This experiment is illustrated in Fig. 7 and Table 3. It indicates that in the presence of water either this or the catalyst or both are consumed during the polymerisation. Reaction 417, IA is the very fast reaction which ensued upon the addition

of moist ethylene dichloride to the reaction mixture when about one half of the first portion of styrene had reacted.

TABLE 3. *Effect of water on the rate of polymerisation of styrene in ethylene dichloride by titanic chloride.*

Expt. No.	Concn. of $TiCl_4$, m.-mole/l.[a]	Concn. of C_8H_8, mole/l.[a]	R,[b] degrees $min.^{-1}$	R_1,[c] degrees $min.^{-1}$ $(mole/l.)^{-2}$
417. I	5·85	0·0771	0·25	42
417. Ia	5·7	~0·04 [d]	~2	1250
417. II	5·65	0·0742	3·3	600
417. III	5·55	0·0729	1·9	360
417. IV	5·50	0·0722	1·2	230
417. V	5·45	0·0715	0·9	180

[a] The concentrations vary because of the increase in volume of the reaction mixture as successive additions are made to it. The volume of styrene added each time was 0·4 c.c. [b] Initial rate corrected for cooling. [c] R corrected to a monomer concn. of 1 mole/l. according to the relation $R \propto [\text{Monomer}]^2$, but not corrected for variation in catalyst concentration. [d] Somewhat less than half the monomer had reacted when the 2 c.c. of $C_2H_4Cl_2$ saturated with water was added (see Fig. 7).

These results show that in the absence of adventitious or deliberately added water, styrene is polymerised by titanic chloride in ethylene dichloride, and this reaction is ascribed to the co-catalytic activity of the solvent.

FIG. 6.

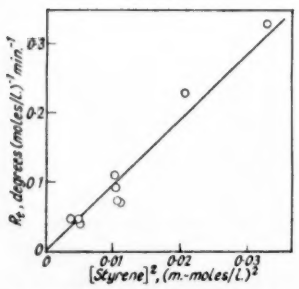

FIG. 7.

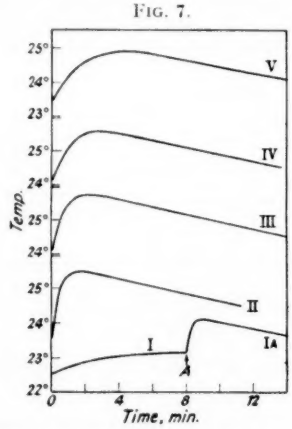

FIG. 6. *Dependence of the first-order rate constant R_1 of the polymerisation of styrene by titanic chloride in ethylene dichloride, on the square of the monomer concentration, at 20°.*

FIG. 7. *Expt.* 417. *The effect of water on the rate of polymerisation of styrene by titanic chloride in ethylene dichloride.*

At *A*, 2 c.c. of ethylene dichloride saturated with water were added to the reaction mixture. Concentrations as in Table 3. Roman numerals indicate successive additions of styrene.

Ethylene dibromide was tried as solvent under the same conditions as with ethylene dichloride. Preliminary experiments showed that in this solvent the polymerisation of styrene by titanic chloride is at least 100 times slower than in ethylene dichloride. The polymerisation is accelerated enormously by small traces of water. Since the reaction rate was so small and not very reproducible, the question whether this solvent can act as co-catalyst remains open.

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340. *The Polymerisation of Styrene by Titanic Chloride. Part II.* The End-groups.*

By P. H. Plesch.

Infra-red spectrographic analysis shows that polystyrenes prepared in various solvents, by titanic chloride as catalyst, have the following features. With toluene as solvent and trichloroacetic acid as co-catalyst, a large fraction of the polymer molecules contain tolyl end-groups. The co-catalyst is not incorporated in the polymer. With titanic chloride only, and ethyl, *iso*propyl, or *tert.*-butyl bromide, or ethylene dichloride as solvents, the polymer is found to contain initial and end-groups derived from the solvent. This is taken to indicate that these solvents can act as co-catalysts. The proportion of terminal double bonds, if they are present at all, is certainly small.

The object of this work was to discover the nature of the end-groups of the polystyrenes formed in different solvents and thus to obtain information about initiation, termination, and transfer mechanisms. The investigation was carried out by means of infra-red spectroscopy and degradation experiments.

Experimental

Materials.—Some of the polystyrenes used were the products of the reactions reported in Part I.* In addition, several specimens were prepared by the techniques described in Part I, and with similar concentrations of styrene and titanic chloride, ethyl, *iso*propyl, or *tert.*-butyl bromide being used as solvent. These materials were purified and dried by standard methods. After the polymerisations, the mixtures were shaken with dilute aqueous sodium carbonate to hydrolyse the titanic chloride, and titanic oxide was filtered off. The infra-red spectra were obtained from polymer films cast from these solutions by evaporation. In order to identify possible bands due to residual solvent, some specimens were separated from their original solvent by steam-distillation and dissolved in benzene, and the films cast from this solution.

Infra-red Spectroscopy.—The spectra of polymers produced in $Pr^{i}Br$ and $Bu^{t}Br$ solution were obtained by Mr. M. St. C. Flett, of Imperial Chemical Industries Limited, Dyestuffs Division, on a Hilger D.209 instrument using single-beam photographic recording. Thin films of the solid materials were used. The spectra of the other polymers were obtained by Dr. G. D. Meakins on the Perkin–Elmer double-beam instrument at Manchester University. The wave numbers recorded are believed to be correct to ± 2 cm.$^{-1}$. The spectra were analysed by a detailed comparison with each other, and with the published spectra of high-molecular-weight polystyrenes. In the Table are recorded all the bands which do not appear in all the spectra, and which are therefore ascribed to characteristic features of the particular polymer, such as end groups.

Results and Conclusions

The main features of all the spectra agree closely with that of polystyrene published by Bryant, Kennedy, and Tanner (*J.*, 1949, 2389). They all have a well-defined band at 1380 cm.$^{-1}$ suggesting the methyl group. The Table shows that there are characteristic differences between the spectra of the different specimens which must be ascribed to different end-groups. It follows that these must be derived from the solvent, and it has indeed been possible to interpret the differences in this way by means of the now well-known band assignments.

1. *Solvent, toluene; co-catalyst, trichloroacetic acid.* Strong bands at 820, 1020, 1515, and 1890 cm.$^{-1}$ indicate *para*-disubstitution. The weaker bands between 1000 and 1200 cm.$^{-1}$ support this. There is no evidence for *ortho*- or *meta*-disubstitution. The strong band at 730 cm.$^{-1}$ may be due to the presence of a (possibly substituted) phenyl group attached to $\cdot CH_2\cdot$ (McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318). The

* Part I, preceding paper.

band lies just outside the limits given by these authors (737—747 cm.$^{-1}$) for $C_6H_5 \cdot CH_2 \cdot$. A strong band at 2970 cm.$^{-1}$ indicates the presence of CH_3 groups. The absence of any distinctive features in the 770 cm.$^{-1}$ region shows the absence of $CH_3 \cdot CH_2 \cdot$ groups. Oxidative degradation of these polystyrenes gave a small yield of terephthalic acid (subl. about 300°) [dimethyl ester (first m. p. 136—139°, on re-melting 140—141°)].

(The symbols +, ++, +++ mean that the bands are weak, moderate, and strong respectively. The strength is assessed qualitatively, partly in relation to the intensity of absorption in the immediate vicinity of the band; 0 means that the band is absent; — means that the relevant region was not recorded.)

	Solvent				
Wave no., cm.$^{-1}$	PhMe	EtBr	$C_2H_4Cl_2$	Pr^{i}Br	Bu^{t}Br
678	0	+++	+++	—	—
728	+++	0	0	—	—
798	+	0	0	0	0
820	+++	0	0	0	0
850	0	0	0	0	++
927	0	0	0	0	+
1020	+++	0	0	0	0
1045	++	0	0	0	0
1060	++	0	0	0	0
1070	0	+++	+++	+++	+++
1080	++	0		0	1078 +++
~1100	0	0	0	+	0
1115	++	+	0	0	0
1122	++	0	+	0	0
~1130	0	0	0	+	0
1235	0	0	0	0	+++
1250	0	0	+	0	0
1260	0	+	0	+	++
1365	0	+	+	0	+++
1380	+++	+++	+++	1370—1380 ++	0
1480	0	+++	+++	++	—
1515	+++	0	0	—	—
1540	0	+	+	—	—
1890	+	0	0	—	—
2970	+++	+	+	—	—

These results indicate the presence of *p*-dialkylphenyl groups in the polymers. Since these are only found in polystyrenes produced in toluene solution, it is concluded that they are due to *p*-tolyl groups. These may be present as end-groups, due to the reaction

$$\sim CH_2 \cdot \overset{+}{C}H \cdot C_6H_5 + C_6H_5 \cdot CH_3 \longrightarrow \sim CH_2 \cdot CH(C_6H_5) \cdot \overset{+}{C}_6H_5 \cdot CH_3$$

followed by the proton-transfer reaction

$$R \cdot \overset{+}{C}_6H_5 \cdot CH_3 + CH_2{:}CH \cdot C_6H_5 \longrightarrow R \cdot C_6H_4 \cdot CH_3 + CH_3 \cdot \overset{+}{C}H \cdot C_6H_5$$

Or they may be present as initial groups due to the reactions

$$\sim CH_2 \cdot \overset{+}{C}H \cdot C_6H_5 + C_6H_5 \cdot CH_3 \longrightarrow \sim CH_2CH_2 \cdot C_6H_5 + \overset{+}{C}_6H_4 \cdot CH_3$$

$$\overset{+}{C}_6H_4 \cdot CH_3 + CH_2{:}CH \cdot C_6H_5 \longrightarrow CH_3 \cdot C_6H_4 \cdot CH_2 \cdot \overset{+}{C}H \cdot C_6H_5$$

It is not possible to decide definitely between these alternatives. The band at 730 cm.$^{-1}$ and the presence of terephthalic acid in the oxidation products make the second one appear rather more plausible. The spectra provide no evidence for the presence of trichloroacetate end-groups derived from the co-catalyst as was found for poly*iso*butenes (Flett and Plesch, *J.*, 1952, 3355). This agrees with the kinetic results, which gave no indication that the co-catalyst was consumed during the polymerisation.

2. *Solvent, ethyl bromide.* The spectra of the polystyrenes prepared in this solvent show only few distinctive bands. The strong band at 678 cm.$^{-1}$ has been assigned tentatively to a C–Cl or possibly a C–Br bond. The presence of halogen was confirmed analytically. The band at 755 cm.$^{-1}$, present in all polystyrenes and due to the $C_6H_5 \cdot CHRR'$ group, is markedly broadened towards 740 cm.$^{-1}$ in these spectra. This,

and the bands at 1070 and 1480 cm.$^{-1}$, indicate the presence of at least two CH_2 groups with a terminal CH_3. These features have therefore been assigned to the $CH_3{\cdot}CH_2{\cdot}CH_2$ group. This is consistent with the theory that the alkyl halide acts as co-catalyst according to the reaction

$$Et + TiCl_4Br^- + CH_2{:}CH{\cdot}C_6H_5 \longrightarrow CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{C}H{\cdot}C_6H_5 + TiCl_4Br^-$$

and that the chain is terminated by the reaction

$$-CH_2{\cdot}\overset{+}{C}H{\cdot}C_6H_5 + TiCl_4Br^- \longrightarrow -CH_2{\cdot}CH(C_6H_5)Cl + TiCl_3Br$$

The solvent may also be involved in an analogous chain-transfer reaction giving rise to the same end groups. This will be discussed in Part III (following paper).

3. *Solvent, ethylene dichloride.* The bands at 678, 1070—1080, and 1480 cm.$^{-1}$ are given the same assignment as in the polystyrenes prepared in ethyl bromide. This is consistent with an initiation and termination mechanism analogous to that illustrated above for ethyl bromide, ethylene dichloride acting as co-catalyst. The fact that in the spectra of these polymers there is a prominent methyl band at 1380 cm.$^{-1}$ and a slight shoulder near 2970 cm.$^{-1}$ shows that some chains must have been started by a proton transfer reaction.

4. *Solvent,* tert.*-butyl bromide.* The bands at 927, 1235, 1260, and 1365 cm.$^{-1}$ indicate unambiguously the presence of *tert.*-butyl groups. This can be accounted for by a mechanism analogous to that suggested for ethyl bromide.

5. *Solvent,* iso*propyl bromide.* The presence of *iso*propyl groups in the polymer is made very probable by the bands at 1020 and near 1100, 1130, and 1480 cm.$^{-1}$, and the fact that the methyl band is very broad (1370—1380 cm.$^{-1}$). This suggests that this compound, too, can act as co-catalyst in the polymerisation of styrene by titanic chloride.

6. *General features.* It is noteworthy that none of the spectra of polystyrenes prepared in alkyl halide solvents shows any sign of disubstituted benzene rings. It has been shown that in poly*iso*butene there is a high degree of terminal unsaturation (Dainton and Sutherland, *J. Polymer Sci.*, 1949, **4**, 37; Flett and Plesch, *Proc. Roy. Dublin Soc.*, 1950, **25**, 150; *loc. cit.*) arising from the loss of a proton from a carbon atom next to the carbonium ion at the growing end of the polymer. If the same process occurred in the cationic polymerisation of styrene, the corresponding terminal groups would be $\cdot CH{:}CH{\cdot}C_6H_5$. In aliphatic compounds this type of double bond has a characteristic absorption band at 965 cm.$^{-1}$; in *trans*-stilbene there are bands at 964 and 986 cm.$^{-1}$ (Brackman and Plesch, *J.*, 1952, 2188). In all the polystyrenes examined here, there are three weak bands at 940, 965, and 980 cm.$^{-1}$. The relative intensities of the first and the third of these are the same in all spectra, whereas the intensity of the middle band varies considerably in relation to those of its neighbours. This band at 965 cm.$^{-1}$ might therefore be associated with terminal unsaturation. However, it also appears in the spectra of high-molecular-weight polystyrenes prepared by free-radical catalysis (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **41**, 246; Bryant, Kennedy, and Tanner, *loc. cit.*). It is possible that even the material of high molecular weight used by these authors contained sufficient unsaturated low polymer, and that this band is indeed due to the suggested group. Moreover, this group should give rise to two bands between 1600 and 1700 cm.$^{-1}$. Although all our spectra and the published spectra show a weak, broad band near 1650 cm.$^{-1}$, it is doubtful whether this can be ascribed to a C=C bond. Thus, we conclude that even if there are terminal double bonds in these polymers, their number must be small. A detailed discussion of this feature will be given in Part III (following paper).

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341. *The Polymerisation of Styrene by Titanic Chloride. Part III.* Discussion.*

By P. H. Plesch.

The results presented in Parts I and II are discussed. It is concluded that styrene cannot be polymerised by titanic chloride in the absence of a co-catalyst. Polymerisation induced by this halide and trichloroacetic acid in toluene solution yields low polymers with terminal tolyl groups, *i.e.*, toluene acts as a transfer agent. It is shown that certain alkyl halides and nitrobenzene may act as co-catalysts. Some of the ways in which a solvent may influence cationic polymerisations are discussed. A new nomenclature for various types of transfer reaction is suggested.

In Parts I and II (preceding papers) some new kinetic and analytical data on the formation of polymers from styrene under the influence of titanic chloride have been presented. These show that there are phenomenological differences between the polymerisations taking place in polar and in non-polar solvents. We therefore discuss these two types of system separately, and then consider, quite generally, some of the possible functions of the solvent in cationic polymerisations.

Non-polar Solvents.—Clark's work (see "Cationic Polymerisation and Related Complexes," ed. P. H. Plesch, Heffer and Sons, Cambridge, 1953, p. 99) has shown that the polymerisation of styrene by boron fluoride in carbon tetrachloride only takes place in the presence of a co-catalyst, such as water. Using the same catalyst and solvent, Brackman and Plesch (*J.*, in the press) obtained the same result with *cis*- and *trans*-stilbene. With alkenes, similar results have been established for some time (for detailed references see *op. cit.*). The present results obtained with styrene and titanic chloride and with hexane and toluene as solvents support the view that styrene can only be made to polymerise by metal halides in the presence of a co-catalyst. The small and variable residual reactivity found in the present work, and previously by Pepper (*Trans. Faraday Soc.*, 1949, **45**, 397, 404) with similar systems, is ascribed to adventitious co-catalyst, probably water. Jordan and Mathieson's claim (*J.*, 1952, 611) that styrene can be polymerised by aluminium chloride without a co-catalyst, cannot be accepted at its face value, and has indeed been severely criticised (*op. cit.*, p. 93). The present work, like that of Williams (*J.*, 1940, 775, Table I, Expts. Nos. 15 and 22) shows once again the importance of an adequate purification technique.

The kinetic results obtained in the present work with toluene as solvent are not sufficient for the deduction of a reaction scheme. However, in conjunction with the analytical and spectroscopic results, they indicate clearly that a co-catalyst is essential, and that the co-catalyst trichloroacetic acid is not incorporated in the polymer. This is in contrast to the results obtained with the system *iso*butene–titanic chloride–trichloroacetic acid–hexane, for which it was found that the co-catalyst is incorporated in the polymer as an end-group (Flett and Plesch, *J.*, 1952, 3355).

Furthermore, the spectroscopic and analytical evidence presented in Part II shows that the polystyrene chains contain a *p*-tolyl group. The low molecular weight of the polymer and the fact that polymerisation goes to completion indicate that the toluene must be involved in a reaction which terminates the physical, but not the kinetic, chain. For this there are at least two possible processes which may be represented thus :

$$RC^+ + S \longrightarrow RCS^+; \qquad RCS^+ + M \longrightarrow RCS + HM^+$$

and

$$RC^+ + S \longrightarrow RCH + S^+; \qquad S^+ + M \longrightarrow SM^+$$

where RC^+ represents the growing polymer, S the transfer agent (toluene in this instance), RCH and RCS are saturated, dead polymer, and M is the monomer. Both mechanisms represent "solvent transfer;" they are, however, sufficiently distinct to merit special

* Part II, preceding paper.

nomenclature, and it is proposed to designate the first Tr-t (transfer with chain termination by the transfer agent), and Tr-i (transfer with initiation by the transfer agent). A third mode of transfer, without incorporation of the transfer agent in the polymer, may be represented thus:

$$RC^{+} + S \longrightarrow RC^{*} + HS^{+}; \quad HS^{+} + M \longrightarrow S + HM^{+}$$

This may be designated Tr-ps (transfer of a proton by the transfer agent): RC* is an unsaturated or cyclised polymer. Kinetic chain transfer without extraneous transfer agent, *e.g.*, proton transfer, will be called Tr-pd (transfer of a proton directly), and may be represented thus: $RC^{+} + M \longrightarrow RC^{*} + HM^{+}$. Some preliminary evidence for this type of transfer has been provided by several workers (*e.g.*, Evans and Meadows, *J. Polymer Sci.*, 1949, **4**, 359; Meier, *J.*, 1950, 3656; Flett and Plesch, *loc. cit.*). It has been pointed out in Part II that, for the system under consideration here, it is not possible to decide whether the toluene is incorporated in the polystyrene by the Tr-i or the Tr-t mechanism.

Studies on the isomerisation of paraffins have shown that aromatic substances can act as chain-breakers in carbonium-ion reactions (Pines, Aristoff, and Ipatieff, *J. Amer. Chem. Soc.*, 1949, **71**, 749), but in polymerisations this has not been observed previously. The appreciable basicity of alkylbenzenes, well known from other reactions, suggests that styrene itself, or indeed polystyrene, might react in the same way as toluene. There is no evidence so far that they do, but for polymerisations carried out at high monomer concentrations it is a possibility which must be taken into account. The resulting polymers would be expected to have distinctive rheological properties, because reaction of a growing chain with a phenyl group on a "dead" chain would lead to branching (and a Tr-pd transfer); reaction of a growing chain with the ring of a monomer molecule would lead to what might be called a "perverse" propagation giving the following unit in the chain, $-CH_2{\cdot}CHPh{\cdot}C_6H_4{\cdot}CHMe{\cdot}CH_2{\cdot}CHPh-$.

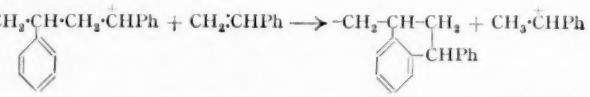
This kind of attack on the phenyl group would only be expected to take place at very high monomer concentrations, and/or with good alkylation catalysts such as aluminium chloride. It has indeed been found by Jordan and Mathieson (*J. Polymer Sci.*, 1952, **9**, 286) that polystyrenes produced with aluminium chloride as catalyst in carbon tetrachloride obey a molecular weight–viscosity relation which differs from that applicable to polystyrenes prepared under the influence of stannic chloride in ethylene dichloride (Pepper, *ibid.*, 1951, **7**, 347). The reason for this might lie in branching or perverse propagation.

In order to shed some light on this question, some polystyrenes prepared from 1·74M-solutions of monomer in ethylene dichloride and in benzene by the action of stannic chloride were obtained by the courtesy of Dr. D. C. Pepper. The spectra of these polymers gave no indication of the presence of disubstituted benzene rings, but they did show a strong absorption band near 1220 $cm.^{-1}$, not found in other polystyrene spectra, which may indicate a quaternary carbon atom. This type of branching in ionically produced polystyrenes must be due to an entirely different process. It may well indicate a hydride-ion transfer reaction analogous to that found for polypropenes by Fontana (*op. cit.*, p. 122); Plesch (*op. cit.*, p. 132) has shown that its occurrence in polystyrenes might be expected. The absence of terminal unsaturation in these polymers is intelligible in terms of the suggested transfer reactions.

Alkyl Halide Solvents.—With ethylene dichloride as solvent the kinetics of the polymerisation agree qualitatively with those which Pepper established for the same solvent and monomer, but with stannic chloride as catalyst (*loc. cit.*). A reaction scheme similar to that suggested by Pepper therefore seems applicable. The present results differ from his in that the third-order rate constant is about two powers of ten greater than that found by him, and that he found small amounts of water to have no appreciable effect on the rate of polymerisation. Although at this stage no exact significance can be attached to the magnitude of the difference between the rate constants obtained with stannic and with titanic chloride, it is in general agreement with other observations which show titanic chloride to be the more powerful catalyst (Fairbrother and Seymour, quoted by Plesch, Polanyi, and Skinner, *J.*, 1947, 257; Russell, *op. cit.*, p. 115). The second discrepancy

concerning the effect of water is not easy to explain. It has been discussed in some detail (*op. cit.*, p. 70) without, however, being resolved unambiguously.

The present kinetic results indicate that polymerisation of styrene can be catalysed by titanic chloride in ethylene dichloride in the absence of water. However, Pepper's recent discovery, that in this solvent hydrochloric and hydrobromic acid will catalyse this polymerisation (*op. cit.*, p. 75), casts doubt upon this interpretation of the results; it is at least possible that in the present experiments the real catalyst was not the metal halide but adventitious hydrochloric acid contained in the titanic chloride solution. The catalysis of cationic polymerisation by hydrogen halides depends upon the cations and anions being separate kinetic entities, and therefore the reaction rate would be expected to be proportional to the $\frac{3}{2}$ power of the monomer concentration and the square-root of the catalyst concentration. This is evidently not the case, and it thus seems very unlikely that in these reactions the real catalyst was hydrogen chloride. It is concluded therefore that chain initiation is due to $Cl{\cdot}CH_2{\cdot}CH_2^+$ ions formed by the interaction of the solvent with the metal halide. The infra-red spectra of the polymers support this conclusion. Spectroscopic results also indicate that polystyrene chains may be started by Et^+, *iso*-Pr^+ and *tert.*-Bu^+ ions. They also show that all the polymers contain methyl groups; for those prepared in ethylene dichloride this must be ascribed to a Tr-pd reaction. The terminal unsaturation, however, which might be expected to accompany such a transfer reaction is notably absent. This may be explained if it is assumed that the transfer reaction is accompanied by cyclisation :



It is well known that polystyrenes produced by cationic catalysis lack unsaturation; and the cyclisation reaction suggested here has been found by Schöpfle and Ryan for 1 : 1-diphenylethylene (*J. Amer. Chem. Soc.*, 1930, **52**, 4021), by Bergmann *et al.* (*Ber.*, 1931, **64**, 1493) and Dainton *et al.* (*op. cit.*, p. 80) for α-methylstyrene, and has been suggested for stilbene by Brackman and Plesch (*J.*, in the press; *op. cit.*, p. 103). An alternative reaction which will account for all the observed features involves yet another type of transfer reaction with the solvent, which will be called Tr-ti, because fragments of the solvent act as chain terminator and initiator. For an alkyl halide RX :

$$-CH_2{\cdot}\overset{+}{C}HPh + RX \longrightarrow -CH_2{\cdot}CHPhX + R^+; \qquad R^+ + CH_2{:}CHPh \longrightarrow R{\cdot}CH_2{\cdot}\overset{+}{C}HPh$$

Much more detailed analytical work is required to decide whether, and to what extent, these alternative reactions take place in each particular system. In view of the fact that titanic chloride can, like aluminium chloride, catalyse aromatic alkylations (Stadnikoff and Kaschtanoff, *Ber.*, 1928, **61**, 1389; Cullinane, *op. cit.*, p. 89), the solvent fragments identified spectroscopically in the polymer might be due to ring alkylation. That this is not so is shown conclusively by the absence of any absorption bands indicative of disubstituted benzene rings.

The co-catalytic activity of alkyl halides in the polymerisation of styrene by titanic chloride links this reaction with the polymerisation of propene by aluminium bromide for which *iso*propyl bromide is a co-catalyst (Fontana *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3745; *op. cit.*, p. 122) and with the cationic isomerisations of hydrocarbons for which alkyl halides also act as co-catalysts (Pines *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1742; 1951, **73**, 5738).

Function of the Solvent.—The importance of the dielectric constant of the solvent in ionic polymerisations was first pointed out by Pepper (*Nature*, 1946, **158**, 789; *Trans. Faraday Soc., loc. cit.*) and later by George, Mark, and Wechsler (*J. Amer. Chem. Soc.*, 1950, **72**, 3891, 3896; *J. Polymer Sci.*, 1951, **6**, 525). Both groups of workers (using styrene and stannic chloride) showed that there appeared to be a linear relation between the logarithm of the polymerisation rate and the dielectric constant (D.C.) of the solution, at least over a limited range of D.C. However, a closer examination of Pepper's work,

and a comparison with that of George *et al.*, shows that this relationship, so far from being unique, is a function not only of the polar, but also of the non-polar, component of the solvent mixtures. Pepper's data show that the rate of polymerisation of styrene in a benzene–ethylene dichloride mixture of D.C. 8·5 is over 100 times greater than in a benzene–nitrobenzene mixture of the same D.C. Since it has been shown (Pepper, *loc. cit.*; Overberger *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 5541; *op. cit.*, p. 106) that the polymerisation in these systems is relatively insensitive to traces of water, this difference in rate in the two solvents indicates a more direct participation of the solvent in the polymerisation reaction than had been suspected before. This is supported by a comparison of Pepper's results with those of George *et al.* concerning the effect of D.C. on the polymerisation rate of styrene in benzene–nitrobenzene and in carbon tetrachloride–nitrobenzene, respectively. At corresponding values of the D.C. the rates are consistently very much greater in the latter mixtures than in the former, and so is the slope of the (log Rate)–D.C. plot. Although a detailed comparison of the results of different groups of workers is probably unjustified at present, yet these very large differences suggest strongly that the non-polar component of the solvent mixture may also influence the reaction.

The above-mentioned phenomena may be explained as follows: (1) Ethylene dichloride acts as a co-catalyst, giving a certain concentration of $CH_2Cl{\cdot}CH_2^+$ ions, but nitrobenzene combines with the catalyst (Reihlen and Hake, *Annalen*, 1927, **452**, 47) and, being in large excess, only leaves very little metal halide free to combine with adventitious co-catalyst; or the nitrobenzene–stannic chloride complex is itself catalytically active, but weak, giving only a small concentration of ions:

$$SnCl_4 + Ph{\cdot}NO_2 \rightleftarrows SnCl_4,O_2N{\cdot}Ph, \quad [SnCl_4]_{free} \text{ small}$$

$$SnCl_4,O_2N{\cdot}Ph \rightleftarrows SnCl_4,O_2N{\cdot}C_6H_4^-H^+, \quad [H^+] \text{ small}$$

(2) Whereas nitrobenzene appears to be a poor co-catalyst (see *op. cit.*, p. 89), carbon tetrachloride may be a much better one. Unfortunately, there is no direct evidence for this supposition, but there are related phenomena which support it (see *op. cit.*, p. 97), *e.g.*, the addition of carbon tetrachloride to double bonds, catalysed by aluminium chloride.

Co-catalysis by nitrobenzene explains very simply why water has little effect on the cationic polymerisations proceeding in this solvent: the mass-action effect would keep most of the metal halide combined with the solvent. It is noteworthy in this context that the co-catalytic activity of aliphatic nitro-compounds is very strong (Schmerling, *Ind. Eng. Chem.*, 1948, **40**, 2072; Russell, *op. cit.*, p. 89), which is intelligible in terms of their pseudo-acidic nature.

The present work, in conjunction with that of other authors, thus shows that in cationic polymerisations a solvent may affect the reaction in the following ways: (1) It may influence (mainly) the initiation and termination steps by electrostatic action (Pepper's dielectric-constant effect). (2) It may form a complex with the metal halide catalyst. This complex may give rise to ions which can initiate polymerisation, *i.e.*, the solvent may act as co-catalyst. If a complex is formed the concentration of free metal halide will be considerably reduced so that a complexing but non-co-catalytic solvent will act as inhibitor. (3) It may act as a transfer agent. Whether a particular solvent can act thus, and the type of transfer which it produces, will depend on the monomer concerned, because the regulating feature in this reaction is the difference between the free-energy changes accompanying the interactions of the polymer ion with the solvent and of the solvent ion with the monomer.

Added in Proof.—Recent work suggests that the polymerisation of styrene in toluene may involve not the tolyl ion as suggested above, but the benzyl ion participating in a Tr-i reaction:

$$RCH_2{\cdot}\overset{+}{C}HPh + MePh \longrightarrow RCH_2{\cdot}CH_2{\cdot}Ph + Ph\overset{+}{C}H_2$$

The presence of *para*-disubstitution in the polymer then requires that this should proceed not only by the obvious route,

$$Ph\overset{+}{C}H_2 + CH_2{:}CHPh \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{C}HPh,$$

but also by the "perverse" route

$$\overset{+}{\text{PhCH}_2} + \text{CH}_2{:}\text{CHPh} \longrightarrow \text{PhCH}_2{\cdot}\text{C}_6\text{H}_4{\cdot}\overset{+}{\text{C}}\text{HMe}.$$

The evidence presented here is consistent with both alternatives.

Most of this work was carried out in the Chemistry Department of the University of Manchester. I am grateful to the late Professor M. G. Evans, F.R.S., for his interest and encouragement; also I thank the University of Manchester for a grant from the Schunk Fund, Messrs. Petrocarbon Ltd. for a gift of pure styrene, Mr. M. St. C. Flett, of Imperial Chemical Industries Limited, and Dr. G. D. Meakins, of Manchester University, for obtaining the infrared spectrograms, Mr. M. Rigbi for assistance with the degradation of polystyrenes, and the D.S.I.R. for a grant which facilitated the completion of this work.

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342. *Thermal Decomposition of Hydrazobenzene, studied by the Use of Nitrogen Isotopes.*

By P. F. HOLT and B. P. HUGHES.

A modified Dumas procedure is a satisfactory alternative to the Rittenberg procedure for the preparation of nitrogen for mass-spectrographic analysis. When decomposed by the Dumas procedure, [^{15}N]azobenzene, labelled in one position, gives nitrogen without complete random pairing of the atoms.

The formation of azobenzene by the thermal decomposition of hydrazobenzene does not involve separation of the nitrogen atoms.

DIARYLHYDRAZINES, or hydrazo-compounds, undergo disproportionation with the production of an azo-compound and an amine or amines: $2\text{R}{\cdot}\text{NH}{\cdot}\text{NH}{\cdot}\text{R}' \longrightarrow \text{R}{\cdot}\text{N}{:}\text{N}{\cdot}\text{R}' + \text{NH}_2\text{R} + \text{NH}_2\text{R}'$, where R and R′ = aryl. This reaction occurs when a solution of the hydrazo-compound in ethanol or another solvent is heated or irradiated with ultraviolet light of wave-length 2300—2700 Å (Weiss, *Trans. Faraday Soc.*, 1940, **36**, 856). Two opposing theories for the thermal decomposition have been suggested.

Stieglitz and Curme (*Ber.*, 1913, **46**, 911; cf. Curme, *J. Amer. Chem. Soc.*, 1913, **35**, 1143) found the reaction to be of the first order with respect to the hydrazo-compound for about 75% of its course; it then deviated from the first-order law. To explain the initial reaction, Stieglitz and Curme suggested either (*a*) initial fission of hydrazobenzene into aniline and the free radical PhN·, the latter dimerising to form azo-benzene, or (*b*) the production, by homolytic fission, of two similar free radicals Ph·NH·, which may give aniline and the radical PhN· which dimerises; in mechanism (*b*) a more complex reaction might yield azobenzene and aniline directly. The first step was considered to be rate-determining in each case, and mechanisms (*a*) and (*b*) are indistinguishable.

Wieland proposed an intermolecular oxidation and reduction: $\text{Ph}{\cdot}\text{NH}{\cdot}\text{NH}{\cdot}\text{Ph} \longrightarrow \text{Ph}{\cdot}\text{N}{:}\text{N}{\cdot}\text{Ph} + 2\text{H}$; $\text{Ph}{\cdot}\text{NH}{\cdot}\text{NH}{\cdot}\text{Ph} + 2\text{H} \longrightarrow 2\text{NH}_2\text{Ph}$. He emphasised that, if the first reaction were rate-determining, first-order kinetics with respect to hydrazobenzene would still be shown. In the presence of a palladium catalyst, the reaction takes place at room temperature and Wieland (*Ber.*, 1912, **45**, 492) then isolated hydrogen from the catalyst. He also pointed out that disproportionation of an unsymmetrical hydrazo-compound should yield unsymmetrical and symmetrical azo-compounds if the views of Stieglitz and Curme were valid. He decomposed 4-methylhydrazobenzene thermally in alcohol but was able to separate only an azo-compound showing the melting point of 4-methylazobenzene, although either of the possible symmetrical azo-compounds was shown to depress the melting point of the unsymmetrical compound.

Little further work has appeared. Goldschmidt's observation that triphenylmethyl reacts with hydrazobenzene to form azobenzene and triphenylmethane (*Ber.*, 1922, **55**, 3217) was said to support Wieland's hypothesis. However, triphenylmethyl is able to

remove hydrogen from many compounds. Although Stieglitz and Curme's kinetic measurements are not conclusive, the free-radical mechanism appears to have found some acceptance: see, for example, Dewar ("Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 42). Weiss (*loc. cit.*) has used a similar free-radical mechanism to explain the photochemical reaction.

The mechanisms suggested by Stieglitz and Curme involve the fission of the nitrogen–nitrogen bond in hydrazobenzene and subsequent formation of azobenzene from the free radicals so produced. The second stage involves the formation of azo-groups by the random pairing of nitrogen atoms. Wieland's mechanism, on the other hand, involves no separation of the nitrogen atoms in the hydrazo-compound. Consequently, when one of the two nitrogen atoms in hydrazobenzene is labelled, the distribution of the two isotopes in the hydrazobenzene and the azobenzene will be identical if the reaction takes place by Wieland's mechanism.

The measurement of nitrogen isotope ratios requires the preparation of gaseous nitrogen from the sample. The Rittenberg procedure ("Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Michigan, 1948, p. 31) usually used to effect this conversion, involves a Kjeldahl digestion which converts the nitrogen into ammonia; from the ammonia elementary nitrogen is derived for mass spectrometry. This procedure produces molecular nitrogen by the random pairing of nitrogen atoms derived from the sample, and consequently it is inapplicable to the present problem. A method is required for the production of nitrogen samples in which at least some of the molecules consist of two nitrogen atoms derived from the same azobenzene molecule. According to Rittenberg (*op. cit.*) the classical Dumas procedure for the determination of nitrogen in organic compounds "cannot be used for the direct preparation of nitrogen for the mass spectrometer since the nitrogen is collected over a solution of 40% KOH which contains nitrogen." In a modified apparatus, nitrogen was prepared from two labelled samples by the Dumas and by the Rittenberg technique: the same atom % ^{15}N values were obtained (Table 1). The modified Dumas technique appears, then, to be satisfactory and does not necessarily produce random pairing of nitrogen atoms.

Samples of nitrogen gas examined in the mass spectrograph normally contain ions derived from the following types of molecules: $^{14}N^{14}N$, $^{14}N^{15}N$, $^{15}N^{15}N$. It can be shown that when random pairing of the nitrogen atoms occurs the ratio, $R = (^{14}N^{15}N)^2/{}^{15}N^{15}N \cdot {}^{14}N^{14}N$, has a theoretical value of 4. Higher values of R indicate that random pairing cannot have occurred for the whole sample.

TABLE 1.

Substance	Furnace temp.	R (Dumas)	Atom % ^{15}N Rittenberg	Atom % ^{15}N Dumas
Complete random pairing				
$C_6H_4(CO)_2{}^{15}NK$	550°	3·62	32·4	32·0
,, ...	550	3·70		32·5
Random pairing only during combustion				
$Ph\cdot{}^{15}N{:}N\cdot CO_2H$	550	5·60	15·4	15·9
$Ph\cdot N{:}{}^{15}N\cdot Ph$	550	5·90	—	15·4
,, ...	470	7·05	—	15·4
,, *	470	7·36	—	15·3
Disproportionation of hydrazobenzene				
$Ph\cdot N{:}{}^{15}N\cdot Ph$	470	7·37	—	15·0
,, ...	470	7·26	—	14·9

* The hydrazobenzene used in the disproportionation was prepared from this specimen.

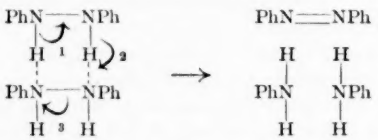
Azobenzene-2-carboxylic acid and azobenzene, both labelled at one nitrogen atom, and potassium [^{15}N]phthalimide, treated by the modified Dumas technique with combustion temperatures of 550° or 470°, gave nitrogen samples having the values of R shown in Table 1. The high values given by the first two compounds, compared with that given by the last, show that random pairing of nitrogen atoms is not complete in the case of these azo-compounds. There is less dissociation of the two nitrogen atoms at the lower combustion temperature.

The values of R obtained by combustion of [^{15}N]phthalimide are lower than the theoretical value of 4, possibly owing to contamination of the sample with carbon monoxide (mass 28). However, the combustion of comparable samples is carried out under standardised conditions and the error from this cause will be sensibly constant. Consequently, the comparison of values obtained from similar samples is permissible.

Disproportionation of Labelled Hydrazobenzene.—A suitable labelled hydrazobenzene is formed by the reduction of the azobenzene, resulting from the condensation of [^{15}N]aniline with unlabelled nitrosobenzene. Disproportionation occurs when the hydrazobenzene in ethanol is kept at 150° for 2 days. Azobenzene samples obtained in this manner yielded nitrogen having values for R of 7·37 and 7·26 (see Table 1). A sample of the azobenzene from which the hydrazobenzene was prepared, and thus having the same isotope distribution, gave $R = 7{\cdot}36$, indicating that randomisation occurs only during the Dumas combustion and that no detectable exchange of nitrogen atoms occurs during the disproportionation.

The experimental results are inconsistent with any mechanism for the disproportionation of hydrazobenzene which requires the fission of the bond between the two nitrogen atoms. The mechanisms proposed by Stieglitz and Curme are, therefore, invalid.

The results are consistent with the mechanism proposed by Wieland or one in which a cyclic dimer is produced and subsequently decomposed :



In the latter case the formation of the exceptionally stable azo-group may initiate the reaction by removing electrons from the N–H link. Subsequent stages are suggested by the arrows in the above scheme. Such association of hydrazobenzene has not been reported although Hunter, by a cryoscopic method, has demonstrated association due to the formation of N–H–N bonds in diazoamino-compounds (*J.*, 1937, 320). Using Hunter's method, we found that hydrazobenzene is associated in benzene solution at 4° (Table 2).

TABLE 2. *Association of hydrazobenzene in benzene solution.*

Molality	0·031	0·041	0·080	0·099
Apparent mol. wt.	186	196	221	237
Association factor, α	1·01	1·06	1·20	1·29

There is no obvious method of measuring the association of hydrazobenzene in ethanol under the conditions used for its disproportionation; presumably association will be reduced because of the preferential formation of O–H–N links with the solvent. Although these cryoscopic measurements suggest that this last mechanism is feasible, Stieglitz and Curme's kinetic measurements do not support it.

EXPERIMENTAL

Combustion of Samples for the Preparation of Nitrogen.—The standard micro-Dumas furnace and filling (Pregl–Grant, "Quantitative Organic Microanalysis," Churchill, 1945, pp. 63—70) are used for the combustion but the nitrometer is modified to facilitate the collection of the gas samples in standard break-seal tubes. The nitrometer tube (see Figure), which is of uniform bore throughout, connects to a T-piece each arm of which can be closed (taps T1, T2, T3). T2 leads to a socket (B10) into which the cone of a sampling tube can be inserted. T1 connects through an alcohol–solid carbon dioxide trap to a vacuum-system (a mercury diffusion pump backed by a mechanical pump). The levelling bulb of the Dumas apparatus is modified to allow for a mercury seal between the potassium hydroxide solution which fills the nitrometer and the atmosphere.

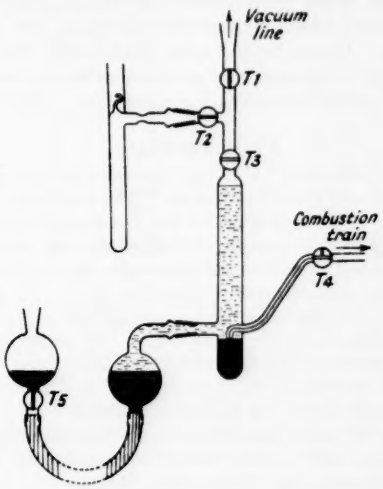
The filling is degassed with T4 open to the atmosphere by passing carbon dioxide through the combustion tube overnight (the gas is prepared by allowing the solid to evaporate slowly in a Dewar flask).

Degassing of the potassium hydroxide solution is commenced about 0·5 hr. before the combustion. Taps T2 and T5 are closed, T1 and T3 are open to the vacuum line. Before the combustion, T3 is closed and T5 is opened until potassium hydroxide solution fills the nitrometer tube. T2 is opened so that one side of T3 is at atmospheric pressure; if this is not done, leaks occur through T3 because this tap is in contact with concentrated alkali. T4 is turned to allow carbon dioxide to pass from the furnace into the nitrometer.

The combustion is effected in the same way as is a micro-Dumas nitrogen determination. After it is complete, the gas remaining in the combustion tube is swept out with carbon dioxide, and then T4 is turned to close the nitrometer.

The break-seal sample tube is then attached to its socket. T1 and T2 are opened to evacuate the tube, then both are closed. T3 is cautiously opened so that a large part of the sample occupies the space between T1, T2, and T3. T3 is closed, and T2 is opened, transferring most of the nitrogen into the sample tube. The last stages of the procedure are repeated if an appreciable amount of the sample remains in the nitrometer. The sample tube is sealed and withdrawn from the apparatus.

[^{15}N]*Azobenzene.*—[^{15}N]Aniline (500 mg.) (Holt and Bullock, *J.*, 1950, 2310) was refluxed with nitrosobenzene (620 mg.) in methanol (10 ml.) and glacial acetic acid (1 ml.) (Mills, *J.*,



1895, 925). Steam-distillation first removed unchanged nitrosobenzene, then azobenzene distilled more slowly. The latter fraction of the distillate was extracted with low-boiling light petroleum, giving azobenzene in 80% yield.

[^{15}N]*Hydrazobenzene.*—[^{15}N]Azobenzene (200 mg.) in dry ethanol (5 ml.) was hydrogenated at normal pressure with a platinum catalyst (5 mg.) until the colour of azobenzene was removed. The solution was cooled in ice, centrifuged to remove catalyst, then immediately transferred to a Pyrex tube, which was cooled in solid carbon dioxide, evacuated, and sealed. The solid was not isolated. The yield, estimated from the final yield of azobenzene, was 90%.

Some [^{15}N]hydrazobenzene was also prepared by the reduction of azobenzene in ethanol with zinc dust and sodium hydroxide. This hydrazobenzene required purification (yield 70—75%).

Disproportionation of [^{15}N]*Hydrazobenzene.*—[^{15}N]Hydrazobenzene (200 mg.) in ethanol (5 ml.), in a sealed Pyrex tube, was heated at 150° ± 1° for 48 hr., then transferred to a distillation flask containing excess of dilute sulphuric acid. Pure azobenzene (75%) was separated by steam-distillation.

We are indebted to Dr. D. H. Tomlin who assayed our nitrogen samples, and to Imperial Chemical Industries Limited, Paints Division, for a grant to one of us (B. P. H.).

THE UNIVERSITY, READING. [*Received, November 6th*, 1952.]

343. *The Crystal Structures of* $ThSe_2$ *and* Th_7Se_{12}.

By R. W. M. D'Eye.

The crystal structures of $ThSe_2$ and Th_7Se_{12} have been determined from powder photographs obtained by use of Guinier-type focusing cameras. $ThSe_2$ is orthorhombic with $a = 4{\cdot}411 \pm 0{\cdot}002$ kX, $b = 7{\cdot}595 \pm 0{\cdot}002$ kX, $c = 9{\cdot}046 \pm 0{\cdot}002$ kX. There are 4 molecules per unit cell and the space-group is D_{2h}^{16}–$Pmnb$. Th_7Se_{12} is hexagonal with $a = 11{\cdot}546 \pm 0{\cdot}006$ kX $c = 4{\cdot}22 \pm 0{\cdot}01$ kX. There is one molecule per unit cell and the space-group is C_{6h}^2–$P6_3/m$. Both compounds are thus isostructural with their corresponding sulphides.

In a recent report (D'Eye, Sellman, and Murray, *J.*, 1952, 2555) of an investigation of the Th–Se system the compounds $ThSe_2$ and Th_7Se_{12} were described. However, owing to the poor powder-diffraction data obtained from Debye–Scherrer photographs it was then not possible to determine unambiguously the crystal structures of these two compounds. Through the courtesy of Professor G. Hägg in allowing me to work at his Institute in Uppsala University, Sweden, it has been possible to obtain good diffraction data by use of Guinier-type focusing cameras which necessarily eliminate the spacing errors caused by absorption in the specimen. It was tentatively suggested in the previous communication that Th_7Se_{12} and $ThSe_2$ had hexagonal and orthorhombic lattices, respectively, and that they were isostructural with their corresponding sulphides. This has now been established.

Experimental

X-Ray photographs were obtained by using Guinier-type focusing cameras with a bent quartz-crystal monochromator and Cu-$K\alpha$ radiation. The intensities of the resulting diffraction lines were visually estimated. The expression for the intensity of a diffraction line on a Guinier-type photograph is $I_c \propto A_1 A_2 p F^2 (1 + \cos^2 2\theta_m \cos^2 2\theta)/\sin^2\theta \cos\theta$, where I_c, θ, θ_m, A_1, A_2, p, and F are respectively the calculated intensity, Bragg angle, the angle the *X*-ray beam from the anti-cathode makes with the monochromator (for Cu, $\theta_m = 13° 21'$), absorption factor for specimen, absorption factor for film emulsion, multiplicity constant, and structure factor (Hägg, personal communication); but for cases where the absorption in the specimen is low (in this case because of the extreme thinness of the specimen) and where extreme accuracy is not required the expression simplifies to $I_c \propto pF^2(1 + \cos^2 2\theta_m \cos^2 2\theta)/\sin^2\theta \cos\theta$, and this expression has been used throughout in calculating intensities.

The diffraction patterns of both compounds were indexed by using the mathematical methods of Hesse (*Acta Cryst.*, 1948, **1**, 200) and of Henry, Lipson, and Wooster ("Interpretation of *X*-Ray Diffraction Photographs," Macmillan, 1951).

Discussion

(1) *Structure of* $ThSe_2$.—The diffraction pattern was indexed on the basis of an orthorhombic lattice with $a = 4{\cdot}411 \pm 0{\cdot}002$, $b = 7{\cdot}595 \pm 0{\cdot}002$, $c = 9{\cdot}046 \pm 0{\cdot}002$ kX. From Table 1 it is seen that the agreement between observed and calculated $\sin^2\theta$ values is good. The number of molecules per unit cell is 4, giving a calculated density of 8·5 g./c.c. (observed, 8·2 g./c.c.). The absences in the observed indices of the reflections indicate that the space-group is D_{2h}^{16}–$Pmnb$. The thorium and selenium atoms will be on the 4(*c*) special position ("International Tables for *X*-Ray Crystallography, Vol. 1). Intensities calculated with the parameters having the values:

	x	*y*		*x*	*y*		*x*	*y*
Th	0·25	0·125	Se_I	0·38	0·43	Se_{II}	0·47	0·82

are seen from Table 1 to be in good agreement with the observed intensities. $ThSe_2$ is therefore isostructural with ThS_2 (Zachariasen, *Acta Cryst.*, 1949, **2**, 291).

The thorium atom is thus surrounded by nine selenium atoms at a mean distance of 3·08 kX [cf. the Th–Se distances in ThOSe and ThSe which are respectively 3·15 and 2·93 kX (D'Eye *et al.*, *loc. cit.*). The individual Th–Se distances (kX) are:

Th–2 Se_I = 2·98	Th–Se_I = 2·85	Th–2 Se_{II} = 3·09
Th– Se_I = 2·93	Th–Se_{II} = 3·22	Th–2 Se_{II} = 3·27

(2) *Structure of* Th_7Se_{12}.—The powder diffraction pattern was indexed on the basis of a hexagonal cell with $a = 11{\cdot}546 \pm 0{\cdot}006$ and $c = 4{\cdot}22 \pm 0{\cdot}01$ kX. The agreement between observed and calculated $\sin^2\theta$ values is seen from Table 2 to be good. If the formula is Th_7Se_{12} there will be one molecule per unit cell, giving a calculated density of 8·7 g./c.c. The compounds ThSe, $ThSe_2$, and ThOSe are all isostructural with their corresponding sulphides. It would therefore seem a reasonable assumption that Th_7Se_{12} is isostructural with Th_7S_{12} (Zachariasen, *loc. cit.*, p. 288). The structure of Th_7S_{12} was

TABLE 1. ($ThSe_2$).

hkl	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	*I*, obs.	*I*, calc.	*hkl*	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	*I*, obs.	*I*, calc.
011	—	0175	—	2	131	1301	1299	w+	38
002	—	0289	—	0	123	1365	1365	w+	18
101	0377	0376	m	35	202	—	1505	—	0
012	0392	0392	s	71	024	1567	1567	w	16
020	0410	0410	m	24	114		1564		0
111	0479	0479	s-	51	033	—	1574	—	1
021		0482		0	212	1612	1608	w	24
112	0694	0696	m	27	040	1637	1640	diffuse vw	—
022		0699		2	133	1877	1879	,, vvw	—
120	0714	0714	w	14	140	1950	1944	,, vvw	—
013	0749	0753	vw	8	141	2019	2016	,, vvw	—
121	0787	0786	s+	100	115	2213	2214	,, vw	—
103	0955	0955	m	52	025		2217		
031	0995	0995	w−	4	231		2211		
122	—	1003	—	2	204	2375	2373	,, w	—
113	1056	1058	m	46	232	2434	2428	,, m	—
023		1061		5	125	2519	2521	,, vw	—
004	1156	1157	w	16	016	2701	2705	,, vw	—
032	1209	1212	s	54	233	2790	2790	,, w	—
200	1217	1216	m	41	052	2858	2852	,, w	—
014	—	1259	—	1	240		2856		

determined from single-crystal data (*idem, ibid.*) and has the space-group C_{6h}^2–$P6_3/m$ with 1 Th on the position 2(*a*) and 6 Th as well as 6 S_I and 6 S_{II} on three positions 6(*h*). The structure exhibits disorder with the one thorium atom on either $00\frac{1}{4}$ or $00\frac{3}{4}$.

It was noted that in the case of Th_7Se_{12} the absences in the observed indices of the reflections were compatible with the space group C_{6h}^2–$P6_3/m$ and the thorium and selenium atoms were accordingly placed on positions 2(*a*) and 6(*c*) and with practically the same parameters as were found for Th_7S_{12}. The parameters used have the values given below:

	x	*y*		*x*	*y*		*x*	*y*
6 Th_{II}	0·15	−0·28	6 Se_I	0·51	0·38	6 Se_{II}	0·24	0·0

Intensities calculated by using these values give fair agreement with the observed intensities, it being borne in mind that the parameters have not been refined for the present case (see Table 2).

TABLE 2. (Th_7Se_{12}).

hkl	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	*I*, obs.	*I*, calc.	*hkl*	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	*I*, obs.	*I*, calc.
010	—	0059	—	0	311	1103	1104	s−	38
110	—	0178	—	0	320	1124	1125	vvw	1
020	—	0237	—	0	410	1242	1243	s	78
101	0392	0393	w	23	041	1279	1281	vw	11
210	0412	0414	s	100	002	1338	1336	vw+	34
111	0512	0512	vw	16	102	—	1395	—	0
030	0530	0533	vw	1	321	1460	1459	diffuse w	24
021	0570	0571	w	41	420	1656	1658	,, m	—
220	0709	0710	vw	3	501	1814	1814	,, vw	—
211	0746	0748	s	80	421	1995	1992	,, w	—
310	0766	0770	vw	4	511	2172	2169	,, w	—
031	0865	0867	s	57	520	2310	2309	,, w	—
040	0948	0947	w−	5	431	2525	2524	,, m	—
221	1044	1044	s−	33	521	2646	2643	,, m	—

Th_7Se_{12} is therefore isostructural with Th_7S_{12}, with Th_1 surrounded by 9 Se_{11} atoms and Th_{11} by 3 Se_{11} and 5 Se_1 atoms. The individual distances can be calculated (in kX) as :

Th_{11}– Se_1 = 3·00	Th_{11}– Se_{11} = 2·89	Th_1–3 Se_{11} = 2·77	
Th_{11}–4 Se_1 = 3·20	Th_{11}–2Se_{11} = 2·92	Th_1–6 Se_{11} = 3·48	Mean Th_{11}–Se = 3·07 kX

The Th_{11}–Se distances are compatible with the Th–Se distances observed in the compounds ThOSe, ThSe, and $ThSe_2$ but the Th_1–Se_{11} distances are either too low or too high. It appears that, as in the case of Th_7S_{12} (Zachariasen, *loc. cit.*), the Se_{11} atoms must be displaced from their mean positions, the direction depending on whether the $00\frac{1}{4}$ or the $00\frac{3}{4}$ position is occupied by the thorium atom. The suggested new Se_{11} positions are given below for the case where the $00\frac{1}{4}$ position is occupied by Th.

6 Se_{11} on 0·27, 0, 0·25; 0, 0·27, 0·25; 0·73, 0·73, 0·25
0·2$\bar{1}$, 0, 0·75; 0, 0·$\bar{2}$1, 0·75; 0·21, 0·21, 0·75

The interatomic distances for Th_1–Se_{11} will now be: Th_1–3 Se_{11} = 3·12 kX, Th_1–6 Se_{11} = 3·20 kX; mean Th_1–Se_{11} = 3·17 kX, which are compatible with other Th–Se distances.

Conclusion.—The results now given add considerable weight to the view expressed earlier (D'Eye *et al.*, *loc. cit.*) that the Th–Se system is closely analogous to the Th–S system (Eastman *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4019).

The author thanks Prof. G. Hägg for valuable advice and interest in the problem and Dr. I. Lindqvist for discussion.

Atomic Energy Research Establishment,
Harwell, Didcot, Berks.

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344. *Larch ε-Galactan. Part II.* The Isolation of 3-β-L-Arabopyranosyl L-Arabinose.*

By J. K. N. Jones.

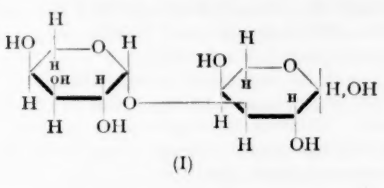
Graded hydrolysis of larch ε-galactan yields a mixture of sugars from which 3-β-L-arabopyranosyl L-arabinose has been isolated and characterised.

L-Arabinose is a common constituent of gums and mucilages and usually occurs, in these substances, in the acid-labile furanose form (cf. Hirst and Jones, *Research*, 1951, **4**, 411). Recently, the pyranose form of L-arabinose has been encountered in Sapote gum (White, *J. Amer. Chem. Soc.*, 1952, **74**, 3966; 1953, **75**, 257). The pyranose form of this sugar is also encountered in the anthocyanins and flavones (*e.g.*, vicianose; Helferich and Bredereck, *Annalen*, 1928, **465**, 166). Previous work (Campbell, Hirst, and Jones, *J.*, 1948, 774; White, *J. Amer. Chem. Soc.*, 1941, **63**, 2871; 1942, **64**, 302, 1507, 2838) had shown that ε-galactan is composed in the main of D-galactopyranose and L-arabofuranose residues, the former predominating. In an attempt to obtain small fragments, the degradation of ε-galactan with hot dilute acid (0·01N) and with cold acid (N) was studied. Examination, at intervals, of the products of hydrolysis on the paper chromatogram showed that arabinose, galactose, and various oligosaccharides were produced. The presence of the latter was demonstrated by spraying the chromatogram with *p*-anisidine hydrochloride and heating it, whereupon several spots, which were either red or brown, appeared. After hydrolysis of the polysaccharide for 1½ hr. at 100°, with 0·01N-hydrochloric acid, the major fraction of the oligosaccharides produced gave the reaction of a pentose and moved more slowly than did galactose. It was isolated by separation of the products of hydrolysis of ε-galactan on columns of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) and identified as 3-β-L-arabopyranosyl L-arabinose (I) on the following evidence,

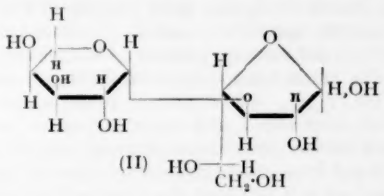
* Part I, *J.*, 1948, 774.

It reduced Fehling's solution, indicating the presence of an aldehyde group, and gave an osazone when heated with phenylhydrazine acetate solution, thus proving the presence of a hydroxyl group on $C_{(2)}$ of the reducing portion of the disaccharide. L-Arabinose was produced on hydrolysis both of the disaccharide and of the osazone. The high positive rotation (+220°) exhibited by (I) in solution indicated that both L-arabinose residues were probably in the pyranose form. On methylation, the disaccharide gave a hexamethyl derivative, which showed an unusually high rotation (+300°); on hydrolysis it gave 2 : 3 : 4-trimethyl and 2 : 4-dimethyl L-arabinose. The trimethyl L-arabinose ($[\alpha]_D$ +120°) was identified by its rate of movement on the chromatogram in butanol–ethanol–water (40 : 11 : 19 by vol.), which is unusually slow for a trimethyl pentose, and as the derived 2 : 3 : 4-trimethyl L-arabonic acid phenylhydrazide. The dimethyl L-arabinose possessed a high positive rotation (+129°) and is therefore a pyranose derivative. This portion of the disaccharide will be methylated on $C_{(2)}$ (see above), and was identified as 2 : 4-dimethyl L-arabinose, since the 2 : 3-dimethyl derivative moves much faster on the paper chromatogram and the 2 : 5-isomer has a negative rotation. This was confirmed by its conversion into the *N*-phenyl-L-arabinosylamine 2 : 4-dimethyl ether (Smith *J.*, 1939, 751) and by its oxidation to a lactone which behaved as a δ-lactone, and therefore possessed a hydroxyl group on $C_{(5)}$. The lactone gave a crystalline phenylhydrazide, but in insufficient amount for characterisation.

The disaccharide probably exists as (II) in the ε-galactan and may have had L-arabofuranose residues attached to the L-arabopyranose portion of the disaccharide. During the formation of the disaccharide (I) by hydrolysis of ε-galactan, it was noted that arabinose and galactose residues were also liberated. This may indicate the presence of galactofuranose residues in ε-galactan. In order to prove that the disaccharide did not arise



(I)



(II)

by resynthesis, a solution of L-arabinose in 0·01N-hydrochloric acid was heated at 100° for 1½ hr. No oligosaccharides were produced.

Gum arabic (Smith, *loc. cit.*), when dissolved in a solution of N-hydrochloric acid and kept for 21 days, was degraded to rhamnose, arabinose, galactose, and oligosaccharides, which were separated by fractionation on cellulose. From the mixture one disaccharide containing arabinose only and a second, very probably 3-α-D-galactopyranosyl L-arabinose, were isolated. The second disaccharide was characterised as its osazone. Derivatives of this disaccharide had been isolated previously and characterised by Smith (*loc. cit.*). Many other gums and mucilages, under these conditions of hydrolysis, yield oligosaccharides containing pentose residues.

As the pairs (*a*) α-D-galactopyranose and β-L-arabopyranose and (*b*) β-D-xylose and β-D-glucuronic acid possess the same configuration of hydroxyl groups on $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ and are often associated with one another, it is possible that enzymes can use either the pentose or the hexose as substrate in (*a*) or (*b*) [cf. the presence of 3-D-galactopyranosyl D-galactose in ε-galactan (White, *loc. cit.*) and the synthesis of 3-α-D-glucopyranosyl L-arabinose from D-glucose-1 phosphate, L-arabinose, and sucrose phosphorylase (Doudoroff, Hassid, and Barker, *J. Biol. Chem.*, 1947, **168**, 733)].

Experimental

The following solvents were used in chromatographic separations on Whatman No. 1 paper: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (*b*) *n*-butanol–pyridine–water (10 : 3 : 3), and (*c*) *n*-butanol–ethanol–water (40 : 11 : 19), all v/v. *p*-Anisidine hydrochloride solution was used as spray to detect sugars. Optical rotations were determined at 20° unless

otherwise stated, and in water. Microanalyses are by Mr. B. S. Noyes of Bristol. Evaporation of solutions was carried out under reduced pressure.

Hydrolysis of ε-Galactan.—Preliminary experiments showed that after 3 weeks ε-galactan (10 g.), dissolved in N-hydrochloric acid (150 c.c.), gave a chromatographic picture [solvent (*b*)] very similar to that obtained after ε-galactan (10 g.) had been heated with 0·01N-hydrochloric acid (70 c.c.) at 100° for 1½ hr. In each case the solution was filtered, neutralised by passage through Amberlite resin IR4B, concentrated, and poured into alcohol. The precipitated, degraded ε-galactan was collected and the filtrate evaporated to a syrupy mixture of sugars (0·7 g.). The syrup was fractionated on a column of cellulose (Hough, Jones, and Wadman, *loc. cit.*), with *n*-butanol half-saturated with water. L-Arabinose appeared first in the effluent, followed by D-galactose, a trace of an unidentified pentose-containing oligosaccharide, 3-β-L-arabopyranosyl L-arabinose (I), and then a hexose-containing disaccharide which gave a brown colour when a sample on paper was heated after spraying. The appropriate fraction of the column effluent containing (I) was collected and concentrated (yield, *ca.* 0·6%).

The material, $[\alpha]_D$ + 220° ± 10° (*c*, 3·4), was chromatographically pure, its rate of movement relative to galactose was 0·79 in solvent (*a*) and 0·69 in solvent (*b*), and, on hydrolysis with N-hydrochloric acid (1 hr.) it gave arabinose only, identified chromatographically. When (I) was heated with phenylhydrazine acetate, an *osazone* was formed (yield 72%), m. p. 235° after recrystallisation from alcohol (Found: C, 57·7; H, 6·0; N, 12·1. $C_{22}H_{28}O_7N_4$ requires C, 57·4; H, 6·1; N, 12·2%).

The disaccharide (0·294 g.) was dissolved in water (5 c.c.) and methylated by the addition of methyl sulphate (1 c.c.), followed by sodium hydroxide solution (2 c.c.; 30%) dropwise, with stirring. When the solution was non-reducing (12 hr.), sodium hydroxide solution (5 c.c.) was added, followed by methyl sulphate (3 c.c.), dropwise. After 24 hr., the solution was heated to destroy sodium methyl sulphate, and the methylated derivative isolated by continuous extraction of the solution with chloroform. Two further treatments, followed by methylation with Purdie's reagents, gave a syrup (0·216 g.), n_D^{15} 1·4710. The product, distilled in a micro-distillation apparatus, had b. p. (bath-temp.) 160—180°/0·05 mm., n_D^{22} 1·4690, $[\alpha]_D$ + 300° (*c*, 1·0) (yield 0·197 g.) (Found: OMe, 48·6. $C_{16}H_{30}O_9$ requires OMe, 50·6%).

The methylated derivative (0·19 g.) was hydrolysed by boiling it in N-hydrochloric acid (20 c.c.): $[\alpha]_D$ +300° (initial value) ⟶ +132° (3 hr., constant value). The solution was cooled, neutralised with silver carbonate, and filtered. Concentration gave a syrup (0·185 g.) which on the paper chromatogram [solvent (*c*)] showed two sugars, which moved more slowly (0·83 and 0·64) than tetramethyl glucose (1·0). The sugars were separated on a sheet of filter paper [solvent (*c*)], and the appropriate sections of paper extracted with acetone. Concentration of the extracts gave 2 : 3 : 4-trimethyl L-arabinose (90 mg.), $[\alpha]_D$ +120° (*c*, 2·0) (Found: OMe, 46·2. Calc. for $C_8H_{16}O_5$: OMe, 48·4%), and 2 : 4-dimethyl L-arabinose (80 mg.), $[\alpha]_D$ +129° ± 4° (*c*, 1·3) (Found: OMe, 34·1. Calc. for $C_7H_{14}O_5$: OMe, 35·3%).

The trimethyl fraction gave an anilide which did not crystallise. A portion (40 mg.) was oxidised with bromine water until the solution was non-reducing. The 2 : 3 : 4-trimethyl L-arabonic acid (32 mg.) was isolated in the usual manner and converted into the phenylhydrazide. The product, after recrystallisation from ethanol, had m. p. 159°, not depressed on admixture with an authentic specimen (Found: N, 9·2; OMe, 30·8. Calc. for $C_{14}H_{22}O_5N_2$: N, 9·4; OMe, 31·2%).

The dimethyl fraction (35 mg.), heated with aniline (20 mg.) in ethanol (2 c.c.), gave in good yield an arabinosylamine derivative, crystallising in plates, m. p. 145—146° after recrystallisation from *n*-butanol (Found: N, 5·6; OMe, 25·1. Calc. for $C_{13}H_{19}O_4N$: N, 5·5; OMe, 24·7%). On oxidation with bromine water, the sugar (35 mg.) gave a lactone, $[\alpha]_D$ +99° (initial value, *c*, 0·85), +88° (1 hr.), +39° (17 hr., constant). Heating it with alcoholic phenylhydrazone gave a crystalline derivative, but in quantity insufficient for analyses.

Hydrolysis of Gum Arabic.—The gum (Turc. variety) (10 g.) was dissolved in N-hydrochloric acid (50 c.c.) and left at room temperature (18° ± 2°) for 21 days. Chromatographic examination of the solution then indicated the presence of arabinose, a trace of galactose, and two oligosaccharides, which moved at speeds (0·41 and 0·33) relative to arabinose (1·0) in solvent (*b*). The solution was filtered and neutralised with Amberlite resin IR4B, and the degraded gum precipitated with alcohol. This material was collected, and the filtrate evaporated to a syrup (2 g.), which was fractionated on a column of cellulose as described above. The effluent was examined chromatographically and the appropriate fractions were collected and concentrated. The major oligosaccharide component was a syrup which showed a rate of movement slower (0·48) than that of galactose (1·0) in solvent (*a*) (yield, 0·11 g.), $[\alpha]_D$ +133° (*c*, 2·1). Heating it

with N-hydrochloric acid for 3 hr. gave an equimolecular mixture of galactose and arabinose. The disaccharide, heated with aqueous phenylhydrazine acetate, gave a *phenylosazone* (in good yield), m. p. 240° after recrystallisation from ethanol (Found: C, 56·2; H, 6·0; N, 11·8. $C_{23}H_{30}O_8N_4$ requires C, 56·4; H, 6·1; N, 11·4%). On hydrolysis of the osazone with boiling N-hydrochloric acid (1 hr.), galactose (detected chromatographically) was liberated.

The author thanks Dr. R. H. Farmer of the Forest Products Research Laboratory for a generous gift of ε-galactan and of European larch sawdust.

THE UNIVERSITY, BRISTOL. [*Received, February 4th*, 1953.]

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345. *The Decomposition of Decalin Hydroperoxide: A Kinetic Study.**

By C. F. H. TIPPER.

The decomposition of decalin hydroperoxide in solution has been investigated under a wide variety of conditions. The overall decomposition was of first order at low concentrations (<0·01—0·03M), and k did not depend on initial concentration. In neutral solvents of low dielectric constant (*e.g.*, decalin, *o*-dichlorobenzene, ethylene glycol), homolytic fission of the hydroperoxide molecules (activation energy ~32—33 kcal.) occurred, followed by a free-radical chain decomposition; and in neutral solvents of high dielectric constant (*e.g.*, nitrobenzene) some ionic decomposition was superimposed on this chain reaction. Addition of water increased the rate of decomposition in acetic acid to a maximum with 60 moles % added. The overall activation energy also increased from 16·7 to 22·1(4) kcal. Probably, addition of water suppressed an induced ionic chain decomposition occurring in the dry acetic acid. The decomposition, though not affected even by strong bases, was subject to acid catalysis in chlorobenzene solution.

HYDROPEROXIDES are now recognised as the most important intermediate in the catalysed and non-catalysed oxidation by molecular oxygen of hydrocarbons in solution. They are formed by a chain mechanism in the first stage of the oxidation, and then decompose or react to give the final products (Bolland, *Quart. Reviews*, 1949, **3**, 1). There is now strong evidence that hydroperoxide decomposition can occur in several ways: (*a*) by molecular rearrangement, (*b*) by an initial split into free radicals, followed usually by a chain reaction, or (*c*) by heterolytic fission, especially in the presence of acids (*e.g.*, see Robertson and Waters, *J.*, 1948, 1578; Kharash, Fono, and Nudenberg, *J. Org. Chem.*, 1950, **15**, 748; 1951, **16**, 113, 128; Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2196). However, little systematic work has been reported on the kinetics of the decomposition of any particular hydroperoxide under widely different conditions. This paper, therefore, presents the results of a kinetic study of the decomposition of decalin hydroperoxide.

Decalin hydroperoxide is an example of a tertiary hydroperoxide with no double bonds or unsaturated rings in the molecule. Its decomposition has apparently not been studied previously, though Criegee (*Annalen*, 1948, **560**, 127) has found that decalin perbenzoate rearranges in solution by an ionic mechanism to give 1-benzoyloxy-1:6-epoxy*cyclo*decane. In the present investigation, low concentrations of hydroperoxide and a colorimetric method of estimation were generally used, since the yield in the preparation was so small.

At least at low concentrations (<0·01—0·03M) the overall decomposition in an inert atmosphere was of first order and k did not vary with the initial concentration. (Fig. 1 shows a selection of the results.) In nearly all cases the rate constants were consistent to within a few units %. However, as the following Table shows, the rate of decomposition was greatly different in different solvents: c is the initial molar concentration, and $t_{\frac{1}{2}}$ the time of half-change (in min.).

* A brief summary of a small portion of this work has been published in *Discuss. Faraday Soc.*, 1951, **10**, 331.

Decomposition of decalin hydroperoxide in various solvents at 130° *(nitrogen was passed through the solution).*

Solvent	10^3c	$t_{\frac{1}{2}}$	Solvent	10^3c	$t_{\frac{1}{2}}$
Chlorobenzene	2·7	§	Nitrobenzene	5·4	244
Butyl alcohol	2·7	†	Ethylene glycol	2·7	70
Decalin	25·3	819 ‡	Pyridine	2·7	~40—50 ‡
o-Dichlorobenzene	2·7	258	Acetic acid	2·7	21 ‡

§ <10% Decomposition in 3 hours. † No appreciable decomposition at 100°.
‡ Obtained by extrapolation of the Arrhenius plot.

Obviously the solvent played an important part in the reaction, and attention was first directed to the neutral solvents of low dielectric constant, which are unfavourable for ionic decomposition.

The overall activation energies for the decomposition in decalin, *o*-dichlorobenzene, and ethylene glycol, calculated from the Arrhenius plots (Fig. 2, *a*, *b*, and *c*), are 32·1, 30·2(5),

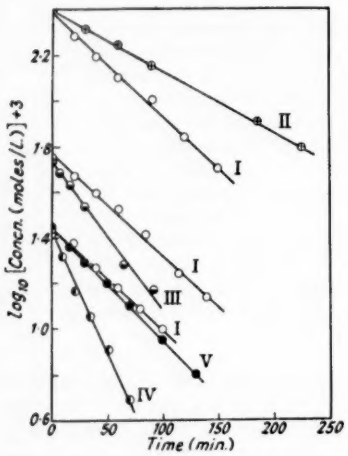


FIG. 1. *Decomposition of decalin hydroperoxide in various solvents. Nitrogen passed through solution. Initial concns.* = 0·025, 0·0054, *and* 0·0027M.

I.	○	Solvent—ethylene glycol.	Temp. = 131·0°.
II.	⊕	,, —decalin.	,, = 151·2°.
III.	◒	,, —nitrobenzene.	,, = 153·5°.
IV.	◐	,, —*o*-dichlorobenzene.	,, = 154·4°.
V.	●	,, —acetic acid.	,, = 109·6°.

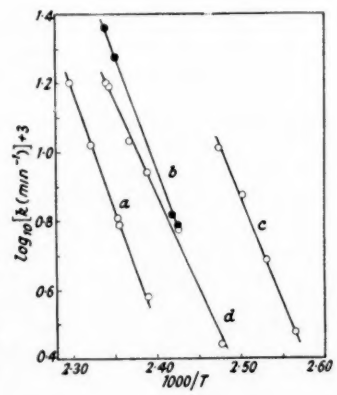


FIG. 2. *Arrhenius plots of the decomposition of decalin hydroperoxide. Nitrogen passed through solution.*

(*a*)	Solvent—decalin.	Initial concn.	= 0·025M.
(*b*)	,, —*o*-dichlorobenzene.	,,	= 0·0027M.
(*c*)	,, —ethylene glycol.	,,	= 0·0027M.
(*d*)	,, —nitrobenzene	,,	= 0·0054M.

and 28·0 kcal., respectively (temperature-independent factors: $8{\cdot}5 \times 10^{13}$, $2{\cdot}2 \times 10^{13}$, and $4{\cdot}0 \times 10^{12}$ sec.$^{-1}$). Thus the order of increasing activation energy is that of decreasing rate of reaction. This suggests that, as k did not depend on the initial concentration of hydroperoxide, the decomposition in these solvents involved a chain mechanism of the same type as that suggested for the decomposition of *p*-anisoyl *p*-nitrobenzoyl peroxide (Leffler, *J. Amer. Chem. Soc.*, **1950**, **72**, 67). There was probably a unimolecular split into free radicals, which reacted with solvent molecules giving solvent radicals. These could have reacted with further hydroperoxide molecules, thus:

(1)	$C_{10}H_{17}\cdot O\cdot OH = C_{10}H_{17}O\cdot + \cdot OH$ (call radicals P)	k_1
(2)	$P\cdot + RX$ (solvent) = PX (HOX or $C_{10}H_{17}\cdot OX$) + $R\cdot$	k_2
(3)	$R\cdot + C_{10}H_{17}\cdot O\cdot OH = RO\cdot C_{10}H_{17} + \cdot OH$ (or ROH + $C_{10}H_{17}O$)	k_3
(4)	$R\cdot + P\cdot$ = inert products	k_4

If we assume that the rate of production of P and R radicals equalled their rate of removal, the overall rate of decomposition is found to be of first order with respect to hydroperoxide

concentration. The overall rate constant is a complicated function of k_1, k_2, k_3, k_4, and the solvent concentration, but the general effect is that the chain reaction decreased the overall activation energy.

The reaction scheme proposed, though probably over-simplified, is supported by the fact that, when hydroperoxides decompose in neutral solvents containing active hydrogen atoms, considerable amounts of the corresponding alcohol together with water are found in the products (see, *e.g.*, Robertson and Waters, *loc. cit.*; Kharasch, Fono, and Nudenberg, *loc. cit.*, p. 116; Bartlett and Cotman, *J. Amer. Chem. Soc.*, 1950, **72**, 3095). Also, it was found that the addition of 0·304 mole/l. of acrylonitrile or 1 : 3 : 5-trinitrobenzene, known to be retarders of free-radical chain reactions, to a 0·0027M-solution of decalin hydroperoxide in ethylene glycol reduced the rate of decomposition considerably at 153·4°. The time of half-decomposition was raised from 10·5 to 27·5 or 60—90 min., respectively. The addition of acenaphthene or ethyl chlorofumarate increased the rate of decomposition somewhat, presumably owing to the radicals produced from these compounds having been more reactive than those from ethylene glycol at the relatively high temperature. Oxygen had no effect at 131°.

The reaction in ethylene glycol catalysed the polymerisation of acrylonitrile, confirming the presence of free radicals. The complete decomposition of 25 ml. of a 0·025M-solution of hydroperoxide in ethylene glycol + 8 vol. % of acrylonitrile gave 0·388 g. of polymer at 131·6°.

Unfortunately, trinitrobenzene, the best retarder, tended to interfere with the analysis of the hydroperoxide, and only qualitative rate measurements, and no determination of the activation energy of the retarded reaction, were possible. However, since the decomposition in decalin was slow even at 153·4° ($t_{\frac{1}{2}}$ = 91·4 min.), and this rate is comparable with the rate in ethylene glycol in the presence of trinitrobenzene, it is likely that only a small amount of induced decomposition occurred in decalin solution. Thus the value for the activation energy of the homolytic fission of decalin hydroperoxide in solution, *i.e.*, of reaction (1), is probably about 32—33 kcal.

Two points concerning the suggested reaction scheme should be considered. First, the results do not preclude the possibility that some decomposition occurred by a molecular mechanism, but the evidence, *e.g.*, of retardation, etc., points to the chain reaction as the more important, if not the only, method of decomposition in these solvents. Secondly, it is always likely, when molecular fission occurs in solution, that the " cage " effect will lead to primary recombination of the fragments. In effect this would reduce the observed rate of decomposition below that calculated on the assumption that bond fission occurred whenever a molecule obtained an energy greater than the activation energy. However, since the temperature-independent factor for the decomposition in decalin was $\sim 10^{14}$, *i.e.*, about the value for " normal " unimolecular decompositions, it seems probable that primary recombination was not marked in this case.

At 117·0° addition of water to the ethylene glycol (thus presumably greatly increasing the dielectric constant of the solvent) caused the rate of decomposition to increase to some extent, though the results were rather erratic. Possibly some ionic decomposition, *e.g.*,

$$(5)\quad C_{10}H_{17}\cdot O\cdot OH = C_{10}H_{17}O^{+} + OH^{-}$$

was occurring together with the free-radical chain reactions.

Removal of traces of impurity from pyridine for use as solvent was very difficult, and thus the results were not consistent and can only be regarded as approximate. The high rate of decomposition of decalin hydroperoxide in pyridine was at first thought to be due to a base-catalysed reaction, especially as addition of water appeared to increase the rate somewhat. However, addition of 0·304 mole/l. of acrylonitrile reduced the rate of reaction at 110° very considerably, and large amounts of polymer (0·536 and 0·804 g., respectively) were formed during the complete decomposition of 25 ml. of a solution of 0·025M-hydroperoxide in pyridine and pyridine–water (40 vol. %) with 8% by vol. of acrylonitrile added. It seems that the high rate and low overall activation energy (<20 kcal.) were due to a very rapid, induced radical decomposition. The decomposition of benzoyl

peroxide is also very rapid in pyridine, and addition of water increases the rate (Tipper, *J.*, 1952, 2966). The addition of 0·4 mole/l. of sodium hydroxide to a 0·0027M-solution of hydroperoxide in ethylene glycol–water (24 : 1 by vol.) had no appreciable effect on the rate of reaction. Hence, decalin hydroperoxide does not undergo base-catalysed decomposition in most circumstances.

With nitrobenzene as solvent, the rate of decomposition at 130° was approximately the same as in *o*-dichlorobenzene, although the overall activation energy was only 24·5 kcal. (Fig. 2, line *d*, shows the Arrhenius plot). Addition of 0·305 mole/l. of acrylonitrile reduced the rate constant at 139·6° from 0·00603 to 0·00357 min.$^{-1}$, this retardation being considerably less than that with ethylene glycol as the solvent at a higher temperature. Thus ionic as well as free-radical decomposition of the hydroperoxide probably occurred owing to the high dielectric constant of nitrobenzene. The anomalous value of the activation energy would then be explained by assuming that the activation energy for heterolytic fission was less than 24·5 kcal. No precipitate was formed when the decomposition took

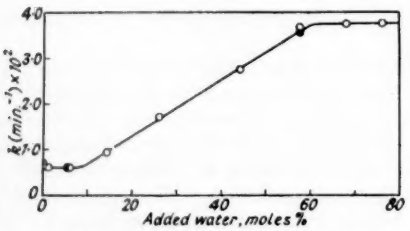


FIG. 3. *Effect of water on the rate of decomposition of decalin hydroperoxide in acetic acid.*
Temp. = 99·75°.
Initial concn. = 0·0027M.
○, Nitrogen passed through solution.
●, Oxygen passed through solution.

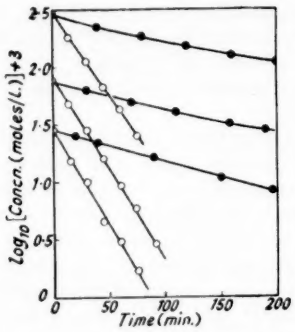


FIG. 4. *Decomposition of decalin hydroperoxide in acetic acid–water mixtures.*
Temp. = 99·3°.
Nitrogen passed through solution.
Initial concns. = 0·0027, 0·0077, *and* 0·030M.
●, 6·1 Moles % H_2O.
○, 67·9 Moles % H_2O.

place in nitrobenzene + 8% by vol. of acrylonitrile, but this may have been due to the molecular weight of the polymer produced having been too low.

The rate of decomposition of decalin hydroperoxide in dry acetic acid at 100° was variable, but the addition of a small amount of water enabled consistent results to be obtained, the value of k being a little lower than with the dry acid. Addition of up to 7—8 moles % of water had no further effect on the rate. Further addition, up to 60 moles %, caused a large increase (~ 6-fold), but still further addition had little effect (Fig. 3).

The decomposition in acetic acid containing 6·1, 26·1, and 67·9 moles % of water was further investigated. With 6·1 moles % the decomposition tended to a higher order than unity at the higher concentrations, though the initial rate was approximately the same, whilst with 67·9 moles % the decomposition was always of the first order but at the highest initial concentration used k was slightly smaller (Fig. 4). The overall activation energies were 16·7, 19·5, and 22·1(4) kcal. and the "temperature-independent factors" were $6{\cdot}1 \times 10^5$, $7{\cdot}7 \times 10^7$, and $5{\cdot}7 \times 10^9$ sec.$^{-1}$ in acetic acid with 6·1, 26·1, and 67·9 moles % of added water respectively (Fig. 5). Additions of acrylonitrile caused little or no retardation of the decomposition (Fig. 5), and only small amounts of polymer were formed (0·170 or 0·029 g., severally) during the complete reaction of 25 ml. of a 0·025M-hydroperoxide solution in acetic acid containing 6·1 or 67·9 moles % of added water and 8 vol. % of added acrylonitrile. The presence of oxygen also had little effect (Fig. 3).

Obviously, little free-radical decomposition was occurring, and probably the first step in the decomposition in aqueous acetic acid was

$$(6)\quad C_{10}H_{17}\cdot O\cdot OH \xrightarrow{H^+} C_{10}H_{17}O^+ + H_2O$$

followed by the rearrangement of the $C_{10}H_{17}O^+$ ion postulated by Criegee (*loc. cit.*):

(7)

The rate of reaction (6) would have increased with increasing water content. The fact that the overall activation energy increased as water was added suggests that this addition was suppressing an induced chain decomposition of the hydroperoxide. It seems likely that

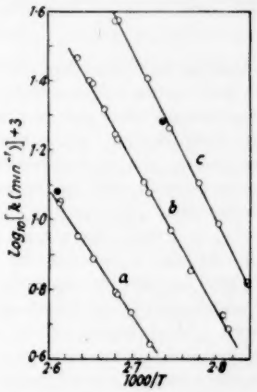
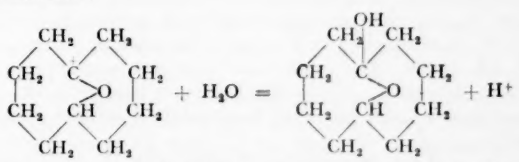


FIG. 5. *Arrhenius plots for the decomposition of decalin hydroperoxide in acetic acid–water mixtures.*

Nitrogen passed through solution.
Initial concn. = 0·0027M.

(*a*) 6·1 Moles % water.
(*b*) 26·1 Moles % water.
(*c*) 67·9 Moles % water.
● 0·305 Mole of acrylonitrile per l. added.

the carbonium ion either attacked an acetic acid or decalin hydroperoxide molecule causing an ionic chain reaction, combined with an acetate ion to give 6-acetoxy*cyclo*decanone, or reacted with a water molecule:

(8) 

It has been found (personal communication from Dr. J. Thomas, Cardiff) that, in general, carbonium ions are not very stable in aqueous media. Reaction (8) must then have predominated in mixtures with a high water content. An ionic chain mechanism has actually been proposed for the decomposition of αα-dimethylbenzyl hydroperoxide in acetic acid (Kharasch, Fono, and Nudenberg, *loc. cit.*, p. 124).

Although decalin hydroperoxide was stable in chlorobenzene for several hours at 117°, yet addition of small amounts of acetic acid caused a decomposition of the first order to occur, the rate being approximately dependent on the square-root of the acid concentration. Addition of chloroacetic acids of greater strength caused increased catalysis, and, except for the very strong trichloroacetic acid, there was a linear relationship between log K_a and log k, as shown by the following table.

The dissociation constants in the table refer to water as solvent at 25°, but their ratios should be the same under the conditions used in this work (Bell, "Acid–Base Catalysis," Oxford, 1941, p. 108). The results are in general agreement with Brønsted's criteria for acid catalysis.

Acid catalysis of the decomposition of decalin hydroperoxide.

Solvent, chlorobenzene. Nitrogen passed through solution. Temp. = 117·2°. Initial concn. of hydroperoxide = 0·0027M.

Acid added	Concn., mole % (m)	K_a for acid	k, min.$^{-1}$	$\sqrt{m}/k$	$[(\log_{10} k) + 1{\cdot}90]/\log_{10} K$
$CH_3{\cdot}CO_2H$	0·394	$1{\cdot}74 \times 10^{-5}$	0·00213	295	0·162
,, ...	1·97	,,	0·00601	233	—
,, ...	4·01	,,	0·00856	234	—
,, ...	8·19	,,	0·0104 0·0101	279	—
$CH_2Cl{\cdot}CO_2H$	0·394	$1{\cdot}38 \times 10^{-3}$	0·00433	—	0·162
$CHCl_2{\cdot}CO_2H$	0·394	$5{\cdot}0 \times 10^{-2}$	0·00774	—	0·163
$CCl_3{\cdot}CO_2H$	0·394	$2{\cdot}0 \times 10^{-1}$	0·0691	—	−1·04

In conclusion, it may be said that homolytic and heterolytic fission of decalin hydroperoxide have been distinguished, and much information on the mechanism of the decomposition obtained, by kinetic measurements, though detailed study of the products formed under various conditions would be required to determine complete reaction schemes.

Experimental

The apparatus and procedure for the kinetic experiments were as described by Tipper (*loc. cit.*). With low initial concentrations, the hydroperoxide content of the samples was determined by the ferrous thiocyanate colorimetric method (Young, Vogt, and Nieuland, *Ind. Eng. Chem. Anal.*, 1936, **8**, 198). This method was used entirely empirically. The ferric compound formed was determined photometrically, the Spekker photometer being calibrated by means of solutions of pure decalin hydroperoxide of known concentration in each particular solvent under investigation. The repeat calibration curves agreed to within 3%. Usually the full colour developed after a minute or two, but when the hydroperoxide was dissolved in nitrobenzene, 15—20 min. were required. When pyridine was used as solvent, it gave a precipitate with the methyl alcohol in which the ferrous thiocyanate was dissolved. This precipitate was filtered off under gravity by means of a coarse, sintered-glass funnel before the depth of colour was measured. With higher initial concentrations the hydroperoxide content was determined by the modified iodometric method of Wagner, Smith, and Peters (*ibid.*, 1947, **19**, 976). Polymerisations were carried out as previously described (Tipper, *loc. cit.*). No polymer was formed under any conditions if no hydroperoxide was present.

Decalin hydroperoxide was prepared from the purified hydrocarbon by Criegee's method (*Ber.*, 1944, **77**, 22). It was found that, if the decalin was oxidised for more than 24 hours at 100°, breakdown products of the hydroperoxide interfered with its separation. It was also found helpful, after shaking the oxidised decalin with sodium hydroxide solution, to shake it with several portions of ethylene glycol as recommended by Cope and Holzmann (*J. Amer. Chem. Soc.*, 1950, **72**, 3062). The crude hydroperoxide was crystallised several times from light petroleum (b. p. 40—60°). The purified product melted at 94—95° and released 98·5—99·5% of the theoretical amount of iodine from acidified sodium iodide. The yield was very small (~0·1—0·2%).

" AnalaR " acetic acid was fractionally distilled with 1% of " AnalaR " anhydride in the presence of nitrogen. Both " AnalaR " and ordinary pyridine were used: they were fractionally distilled twice and then kept at −80° *in vacuo* until required, or were purified by means of the zinc chloride compound (Heap, Jones, and Speakman, *J. Amer. Chem. Soc.*, 1921, **43**, 1936). Other solvents were dried if necessary and fractionally distilled twice in the presence of nitrogen. Decalin was passed down a column of activated silica, and *o*-dichlorobenzene was shaken with concentrated sulphuric acid and then water, before this treatment. The purified solvents were protected from atmospheric damp, and to prevent any oxidation the decalin was kept *in vacuo* at −80° and distilled *in vacuo* before each experiment. 1 : 3 : 5-Trinitrobenzene and acenaphthene were recrystallised from alcohol, amd ethyl chloroformate and dichloroacetic acid were distilled before use. " AnalaR " mono- and tri-chloroacetic acid and " AnalaR " sodium hydroxide were used directly. Nitrogen, oxygen, and acrylonitrile were purified as already described (Tipper, *loc. cit.*).

The author thanks Dr. T. R. Bolam for helpful comments.

Chemistry Department, King's Buildings, Edinburgh, 9. [*Received, December 3rd*, 1952.]

346. *The Vapour Pressure and Lattice Energy of Hydrogen-bonded Crystals. Part I. Oxamide, Oxamic Acid, and Rubeanic Acid.*

By R. S. Bradley and T. G. Cleasby.

The vapour pressure and lattice energy of oxamide, oxamic acid, and rubeanic acid have been determined over the respective temperature ranges 80·4—96·45°, 81·6—90·75°, 86·90—105·15° by an effusion method. It has been shown that oxamide is monomeric in the vapour.

Oxamide, oxamic acid, rubeanic acid (dithio-oxamide), and anhydrous oxalic acid (discussed in Part II, following paper) form an interesting series of hydrogen-bonded molecular crystals. The structures of the crystals, with the exception of oxamic acid, have been studied, but not all are known in detail; oxamide has been studied by Misch and van der Wyk (*Compt. rend. Soc. Phys. Nat., Genève*, 1938, **55**, 96), rubeanic acid by Jeffrey and Markey (to be published), and oxalic acid by Hendricks (*Z. Krist.*, 1935, **91**, 48), and recently also by Cox, Dougill, and Jeffrey, (*J.*, 1952, 4854). It was hoped to make a comparative study of the lattice energies of these crystals, and to make more detailed calculations later.

Experimental

A pure sample of oxamide, obtained from Professor E. G. Cox, was heated *in vacuo* for a few hours at 100° to remove any volatile impurities. Anhydrous oxamic acid (L. Light and Co. Ltd.), purified by vacuum sublimation at 100°, had m. p. 209° (decomp.), and micro-analysis showed that the nitrogen and carbon content agreed with the theoretical to within 1%. Rubeanic acid was purified by crystallisation from pyridine, followed by vacuum sublimation at 100°.

The method for measuring the vapour pressure was similar to that used by Bradley (*Proc. Roy. Soc.*, 1951, **205**, *A*, 553). The rate of effusion of vapour through a small hole in the platinum window of an effusion vessel was determined by means of the loss of weight recorded on a silica micro-balance. The apparatus, shown in Fig. 1, was modified to operate at 80—100° and also to enable a determination of the molecular weight of the vapour to be made, in a manner similar to that of Volmer (*Z. physikal. Chem.*, Bodenstein Festband, 1931, 863). The effusion vessels *A* consisted of soft-glass bulbs with long necks, and carried platinum windows drilled with holes of diameter approx. 1 mm. Thin discs of aluminium rested on the bulbs to act as radiation shields. The bulbs were joined by a rigid arm and were so disposed that the holes were on opposite sides of the arm, so that on effusion of the vapour a torque was applied to the framework. The framework was suspended from a silica micro-balance *B* by a suspension which carried a small galvanometer mirror *C* so that the reflection of a scale in the mirror could be viewed in a telescope. Most of the suspension consisted of stiff silica fibre; the torsion fibre was that carrying the hook of the balance, *i.e.*, a very short thin fibre. Deflections of the micro-balance due to loss in weight could be followed by means of a travelling microscope. The system could be evacuated to less than 10^{-5} mm. The effusion vessel was heated by a double-walled vapour jacket *D*; the temperature was recorded on the Anschütz thermometer lying near the effusion vessel. Normally, when the runs were done at 80—100°, the effusing vapour condensed on the water-cooled joint *E*, but for runs at lower temperatures, *e.g.*, when benzophenone was used for calibration, a cold finger *F*, cooled by acetone–solid carbon dioxide, was used. *G* is a small piece of aluminium foil hung from the effusion vessel in order to reduce oscillations by the use of a powerful magnet brought up to the apparatus.

It was planned to record the torsion and rate of change of weight at almost the same time, but difficulties due to oscillation were met, and the following procedure was adopted. The effusion vessels were filled through the stem and sealed off, the apparatus was assembled, and the balance load adjusted so that the beam swung freely. The balance beam was then pressed down by the arrestment arm *H*, which could be rotated in the ground joint. The pressure was reduced to 1 mm. of mercury and the zero reading of the torsion was taken at room temperature. The magnet was brought up into position, the boiler was started, and after 30 min. the system was evacuated to less than 10^{-5} mm. of mercury. After 15 min. the magnet was slowly withdrawn by means of a platform carrying a rack and pinion, and after 5 min. the reading of the torsion was taken. There was always a small residual oscillation, the limits of which were

recorded. During the whole of this part of the run the beam was held in a fixed position against the arm, so that the torsion hook fibre was always disposed in the same way for repeat runs; the torsional constant of the fibre varied slightly according to the tilt of the beam.

The beam rest was then released, and the oscillations of the beam were damped by suitably moving the beam rest. Deflection–time readings were taken by means of a travelling microscope and a stop-watch, care being taken to read the reference pointer on the balance. The beam was then returned to its fixed position by means of the arrestment; the boiler heater was switched off, 1 mm. of dry air was admitted, and the zero of the torsion checked at room temperature.

The runs using oxamide were calibrated by means of very pure sulphur at 62—63°, with reference to Neumann's data (*Z. physikal. Chem.*, 1934, *A*, **171**, 416). With oxamic and rubeanic acids, for which the vapour pressure alone was studied, benzophenone was used at 38—44°, with reference to Neumann and Volker's data (*ibid.*, 1932, *A*, **161**, 33). In addition, an absolute

FIG. 1.

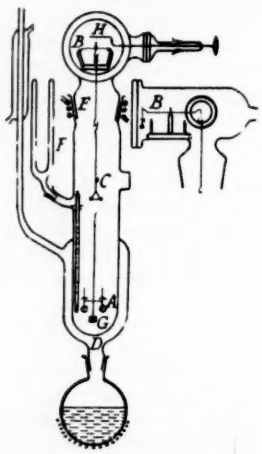
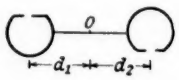


FIG. 2.



determination was made by finding the hole area and thickness photomicrographically. Agreement was obtained with the indirect determination to within 1% after allowance for the tube resistance of the effusion hole by Clausing's method (*Ann. Physik*, 1932, **12**, 961).

Errors arising from an incorrect ratio of hole size to mean free path and from self-cooling were shown to be negligible by the consistent results obtained with effusion vessels of different hole size. This consistency also covers a further possible error due to incorrect ratio of hole size to the surface of the solid in the effusion vessel, for the measured vapour pressure p is always slightly less than the true saturation pressure p_0. The rate of effusion through the hole of area A is equal to the net rate of supply of the vapour in the effusion vessel, or

$$Ap = \alpha A_s p_0 - \alpha A_s p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where A_s is the area of the solid, and α the evaporation coefficient. Hence $p/p_0 = \alpha A_s/(A + \alpha A_s)$. Under the conditions of this research the difference between p_0 and p is negligible. Theoretical calculations of the self-cooling and of the resistance factor due to the balance-case tubing showed that errors due to these factors were negligible. The cooling due to radiation losses from the hot region at 100° to the cold region at room temperature was calculated to be rather less than 1°, but was not allowed for since the temperatures were read on the thermometer inside the case.

Vapour pressures p may be calculated from the rate of loss of mass, $\mathrm{d}w/\mathrm{d}t$, since

$$p = (-\mathrm{d}w/\mathrm{d}t)(2\pi \boldsymbol{R} T/M)^{\frac{1}{2}}/A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where M is the molecular weight, and $\boldsymbol{R}$ the gas constant. This equation may be written

$$p = (-\mathrm{d}w/\mathrm{d}t)T^{\frac{1}{2}}K_1/M^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where K_1 is an apparatus constant determined by calibration by means of sulphur or benzophenone.

The molecular weight may be calculated from the consideration that the recoil force at the holes of effective area A_1 and A_2 is $\frac{1}{2}pA_1$ and $\frac{1}{2}pA_2$ respectively, and that there will be a torque

about the axis of rotation O (Fig. 2). This torque will be $2(\frac{1}{2}pA_1d_1)$ or $2(\frac{1}{2}pA_2d_2)$, whichever is the smaller; any lack of balance between the two torques acting on the separate effusion vessels will act as a force at the fulcrum O, and will not cause rotation about the axis. If the angle of torsion is θ and the torsional constant c, then $c\theta = pA_1d_1$ (the first alternative being taken for the torques), and

$$p = K_2\theta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where K_2 can be found by calibration. Hence

$$M = (-\mathrm{d}w/\mathrm{d}t)^2TK_1^2/(K_2\theta)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Results for oxamide are given in Table 1, and the values of the lattice energy and entropy of vaporisation for the three compounds now examined, together with those for anhydrous oxalic acid (from Part II, for comparison), are summarised in Table 4.

TABLE 1. *Vapour pressures (cm. Hg) of oxamide.*

Effusion vessel 1.				Effusion vessel 1.				Effusion vessel 2.			
	Angle of torsion,	V. p. × 10^5 from			Angle of torsion,	V. p. × 10^5 from			Angle of torsion,	V. p. × 10^5 from	
T	radians	torsion	$-\mathrm{d}w/\mathrm{d}t$	T	radians	torsion	$-\mathrm{d}w/\mathrm{d}t$	T	radians	torsion	$-\mathrm{d}w/\mathrm{d}t$
92·75°	0·175	2·90	2·94	88·60°	0·111	1·88	1·84	96·45°	0·201	4·14	4·09
92·50	0·175	2·90	2·77	88·45	0·112	1·90	1·85	96·40	0·200	4·11	4·14
92·30	0·171	2·84	2·77	88·45	0·111	1·89	1·90	92·05	0·125	2·57	2·59
91·40	0·152	2·58	2·60	80·45	0·0469	0·800	0·802	90·10	0·108	2·21	2·26
90·65	0·145	2·47	2·45	80·40	0·0469	0·800	0·807	88·80	0·093	1·92	1·93
88·70	0·112	1·90	1·88	80·40	0·0487	0·837	0·796	88·55	0·090	1·86	1·89

TABLE 2. *Vapour pressures (cm. Hg) of oxamic acid.*

	Effusion vessel 3.								Effusion vessel 4.		
T	90·00°	88·90°	82·55°	81·60°	78·65°	77·30°	76·00°	75·80°	90·75°	89·90°	82·15°
V. p. × 10^5	11·3	11·1	5·37	4·86	3·52	3·04	2·65	2·65	12·1	11·3	4·95

TABLE 3. *Vapour pressures (cm. Hg) of rubeanic acid.*

	Effusion vessel 5.						Effusion vessel 6.		
T	104·15°	103·75°	102·05°	102·00°	101·60°	98·20°	105·15°	104·25°	98·05°
V. p. × 10^4 ...	12·2	11·8	10·4	10·3	10·2	7·52	14·0	12·8	7·16
T	98·15°	98·05°	94·45°	94·75°	93·35°	86·90°			
V. p. × 10^4 ...	7·56	7·35	5·13	5·35	4·59	2·44			

TABLE 4.

Substance	Lattice energy (cal. mole^{-1})	Entropy of vaporisation (cal. degree^{-1} mole^{-1})
Oxamide	27,000	44·4
Oxamic acid	25,800	44·4
Rubeanic acid	25,200	45·0
Oxalic acid (α) (cf. Part II)	23,400	47·0
Oxalic acid (β) (cf. Part II)	22,300	44·3

Instead of calculating M for oxamide, we have given the vapour pressures calculated from the torsion and loss of weight, the value of M being assumed. The vapour pressure is well represented by the equation $\log_{10} p$(cm. of Hg) $= -5893/T + 11{\cdot}568$. If the molecular weight is calculated from equation (5) a mean value of 87·1 is obtained, in good agreement with the actual value, 88·05, although a scatter of $\pm 5\%$ was observed. It should be remembered, however, that this molecular weight was determined on vapours at very low pressures, and that errors in the determination of θ or $(-\mathrm{d}w/\mathrm{d}t)$ are doubled in the calculation of the molecular weight. (Owing to the low vapour pressure the latent heat of vaporisation may be equated to the lattice energy.)

The vapour pressure of oxamic acid (Table 2) is well represented by the equation $\log_{10} p$ (cm. of Hg) $= -5639/T + 11{\cdot}580$. Results for rubeanic acid are given in Table 3; the vapour pressures are given by $\log_{10} p$ (cm. of Hg) $= -5515/T + 11{\cdot}713$.

Discussion.—The lattice energy of molecular crystals such as oxamide, etc., may be split into the quantum-mechanical dispersion energy, electrostatic interaction energy, and energy of repulsion. Part of this energy may be attributed to the so-called hydrogen bonding between nearest neighbours, but it is not easy to calculate or even define such a contribution in the solid state where the contribution of non-nearest neighbours may be

appreciable, especially to the electrostatic term. The (O···H–O) hydrogen bond energy has usually been estimated for carboxylic acids from the heat of dimerization of the vapours to be approximately 8 kcal. Similarly the N···H–N bond has been estimated from the virial coefficient of ammonia to be 3·8 kcal. (Lambert and Strong, *Proc. Roy. Soc.*, **1950**, *A*, **200**, 566), but this dimerization energy involves a general electrostatic and dispersive interaction between the two molecules, as well as repulsive energy and reorganisation energy of the fragment after the dimer has split into monomers. The danger of neglecting repulsive energy is brought out by Searcy's calculation for ice (*J. Chem. Phys.*, **1947**, **17**, 210), this energy amounting to 42% of the lattice energy of the solid.

It is clear on the basis of two hydrogen bonds per molecule, and the assumption that the " hydrogen bond energy " deduced from the vapour applies to the solid state, that there is a considerable " background energy." The proper analysis awaits a detailed knowledge of the structures, but it is noteworthy that the replacement of CO·OH by $CO{\cdot}NH_2$ increases the lattice energy (cf. oxamic acid and oxamide), which is contrary to what might be expected. The replacement of O by S causes a decrease in lattice energy, in accordance with expectations (cf. oxamide and rubeanic acid). It is possible that part of the lattice energy arises from the presence of some kind of zwitterion, *e.g.*, $NH_3^+ CO{\cdot}CO_2^-$, with the possibility of proton transfer from one potential trough to another, *e.g.*, a CO_2H group of one molecule adjacent to the NH_2 group of another molecule could lose a proton to the NH_2 group; such zwitterions, which might have a transient existence, would increase the electrostatic energy and the melting point, although the so-called resonance energy due to proton transfer would be negligible.

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THE UNIVERSITY OF LEEDS. [*Received, December 11th*, 1952]

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347. *The Vapour Pressure and Lattice Energy of Hydrogen-bonded Crystals. Part II.* α- and β-Anhydrous Oxalic Acid and Tetragonal Pentaerythritol.*

By R. S. BRADLEY and S. COTSON.

The vapour pressures and lattice energies of α- and β-anhydrous oxalic acid have been determined over the respective ranges 37·62—51·91° and 37·62—50·06°. The α-form is stable at room temperature. The transition temperature lies above the decomposition point. Pressures of water vapour in the system β-anhydrous acid–dihydrate–water vapour have been measured at 32·75—46·9°, but no equilibrium was reached with the α-anhydrous acid in the presence of dihydrate and water vapour, because the dihydrate gives the β-acid on dehydration. The vapour pressure and lattice energy of tetragonal pentaerythritol have been determined at 106·4—135·1°. Some preliminary discussion is given of the contribution of hydrogen bonding to the lattice energies of these compounds.

ALTHOUGH the dimorphism of anhydrous oxalic acid has been reported, and *X*-ray studies have been made by Hoffmann and Mark (*Z. physikal. Chem.*, **1924**, **3**, 321) and by Hendricks (*Z. Krist.*, **1935**, **91**, **48**), no reliable indication was found as to which is the more stable form at room temperature, and it was not known whether there was a transition point. It was therefore decided to obtain values of the vapour pressure and thermodynamic data for the two forms, and if possible to relate these data to the structures, which are being studied by other workers in this Department (Cox and Dougill). It was hoped, in addition, to study the vapour pressure of water in equilibrium, metastable or otherwise, with the dihydrate in the presence of either of the two forms. This work is reported in Section (*a*).

* Part I, preceding paper.

With pentaerythritol, Section (*b*), it was convenient to study only the one form, that for which the structure has been determined (Cox, Goodwin, and Llewellyn, *J.*, 1937, 883; Nitta and Watenabe, *Nature*, 1937, **140**, 365), since the transition to the cubic form occurs at 180°.

Experimental

Section (*a*).—The α (orthorhombic) form of anhydrous oxalic acid was prepared by dehydrating "AnalaR" dihydrate *in vacuo* at 100°, admitting dry air, and adding acetone (dried over Na_2SO_4). The solution was placed in a vacuum desiccator [over $Mg(ClO_4)_2$, which absorbed acetone vapour], and deposited crystals overnight.

The β (monoclinic) form was prepared by dehydrating the dihydrate *in vacuo* at 100°, needle-shaped crystals subliming on the cold neck of the flask. This method was more convenient than that of Partington and Johnson (*J.*, 1930, 1510), which involves distillation with toluene; these authors did not specify which form was prepared.

The samples were shown to be pure by titration with potassium permanganate. Both forms had d_4^{18} 1·89, as determined by the flotation method, by the use of mixtures of carbon tetrachloride and ethylene dibromide.

Vapour pressures were determined by an application of Knudsen's effusion method, the apparatus being similar to that described in the preceding paper; the balance case was immersed in a thermostat at 37—52°. Consistent results for the vapour pressure were obtained under a variety of conditions in which the hole size was varied and the cooling medium was changed from solid carbon dioxide and acetone to liquid nitrogen. It was necessary to hang the effusion vessel about 10 cm. from the cold finger and further to protect it by means of a radiation shield of aluminium foil if the vessel was surrounded by tubing 2·5 cm. in radius. It was shown that the errors described in the preceding paper were absent. Benzophenone was used as the calibrating substance, together with Neumann and Volker's data (*Z. physikal. Chem.*, 1931, *A*, **161**, 33), but in addition, an absolute determination was made by measuring the area and thickness of the effusion hole photomicrographically. When allowance had been made by Clausing's method (*Ann. Physik*, 1932, **12**, 961) for the tube resistance of the hole, agreement between the relative and absolute determinations was secured to within 1%. Recalibration at the end of the experiments gave a consistent result.

During the transfer of the samples to the effusion vessel, some hydration necessarily occurred, and this water was lost during the early stages of the evacuation. When the β-acid was studied, the rate of effusion at a particular temperature became constant and reproducible when all this water had been evolved, but with the α-form the apparent vapour pressure decreased in successive runs, becoming constant only after several days. It appears, therefore, that the dihydrate gives the β-acid on dehydration, and that a mixture of the α- and the β-form slowly reverts to the pure α-form. The β is thus the unstable form at room temperatures, in agreement with the higher vapour pressure which we have found for this form. Special precautions had to be taken owing to the ease of hydration of the anhydrous form. When the balance had moved over its range, it was necessary to replace the weight lost by silica; the joint of the balance case was lowered only a few cm., the requisite amount of silica was added to the hook supporting the effusion vessel, and the joint was quickly re-sealed.

Table 1. *Vapour pressures* (*cm.* Hg) *of α- and β-anhydrous oxalic acid.*

Data for α-form						Data for β-form			
Effusion vessel 1		Effusion vessel 2				Effusion vessel 1		Effusion vessel 2	
T	V. p. × 10^4	*T*	V. p. × 10^4	*T*	V. p. × 10^4	*T*	V. p. × 10^4	*T*	V. p. × 10^4
37·62°	0·445	37·81°	0·452	47·37°	1·47	38·60°	0·847	37·62°	0·755
39·12	0·559	41·00	0·669	50·00	1·98	41·96	1·27	40·45	1·03
42·37	0·836	41·71	0·734	51·91	2·45	45·18	1·79	43·40	1·49
45·58	1·21	43·80	0·990	—	—	48·48	2·60	47·02	2·22
48·63	1·74	46·83	1·39	—	—	51·83	3·61	50·06	3·15

The vapour pressures of the α- and the β-form of oxalic acid are given in Table 1. They are given respectively by the equations

$$\log_{10} p = 12{\cdot}17 - 5130/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

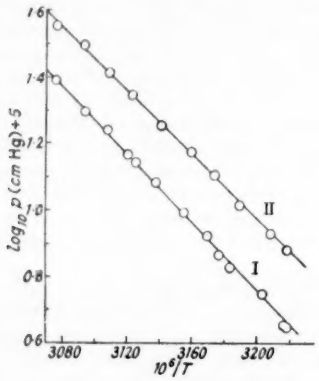
and

$$\log_{10} p = 11{\cdot}57 - 4875/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The two lines are shown in the Figure. The lattice energies of the α- and the β-form are 23,450 and 22,280 cal. mole^{-1}, and the entropies of sublimation 47·0 and 44·3 cal. degree^{-1} mole^{-1}, respectively; owing to the low vapour pressures the lattice energy may be equated to the latent heat of vaporisation. The heat content and entropy change for the transition $\beta \rightarrow \alpha$ are $\Delta H = -1170$ cal. mole^{-1}, $\Delta S = -2{\cdot}7$ cal. degree^{-1} mole^{-1}. The transition temperature, at which the vapour pressures become equal, is 152° according to equations (1) and (2), but this assumes that these equations can be extrapolated to higher temperatures without allowing for the change of heat of vaporisation with temperature. Since oxalic acid decomposes on sufficient heating, the transition point cannot be realised in practice. Noyes and Wobbe (*J. Amer. Chem. Soc.*, 1926, **48**, 1882), who prepared their anhydrous acid by dehydrating the hydrate *in vacuo*, and who must therefore have studied the β-form, give $\log_{10} p_{\text{cm. Hg}} = 11{\cdot}22 - 4727/T$, which gives values of the vapour pressures up to 30% higher than ours.

A determination of the molecular weight of the vapour was made, in order to detect decomposition or association, by the use of the apparatus described in Part I (*loc. cit.*). A value of 91·1 was obtained, showing that no decomposition occurs, and that association is negligible—as would be expected from the low values of the vapour pressures studied.

The pressures of water vapour for the system anhydrous acid–dihydrate–water vapour were measured by means of an accurate wide-bore mercury manometer. With the β-anhydrous acid no difficulty was experienced, and the system came rapidly to an apparent equilibrium



Vapour pressures of anhydrous oxalic acid.
I. α-Orthorhombic. II. β-Monoclinic.

(although the β is the unstable form). The vapour pressures of water are given in Table 2 and are well represented by the equation

$$\log_{10} p_{\text{cm. Hg}} = 9{\cdot}427 - 2995/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

giving a heat of dehydration of 13,700 cal. per mole of water removed. This result agrees well with that of Bell (*J.*, 1940, 72), *viz.*, 13,600 cal., although the values of the vapour pressures obtained by us are about 15% lower than those given by his equation, $\log_{10} p_{\text{cm. Hg}} = 9{\cdot}45 - 2983/T$; Bell's results show, however, considerably greater scatter than ours. Becker and Roth (*Z. Elecktrochem.*, 1935, **40**, 836) have calculated the heat of hydration from thermochemical data to be 3300 cal. per mole of water, giving ΔH for the dehydration 13,300—13,440 cal. per mole of water, the variation allowing for the temperature change of the heat of vaporisation of water.

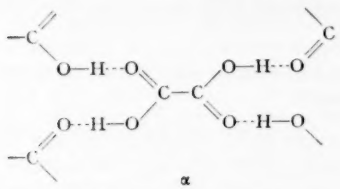
TABLE 2. *Pressure of water vapour (cm. Hg) for the system β-oxalic acid–dihydrate–water vapour.*

T	32·75°	35·30°	39·95°	42·00°	44·50°	46·90°
Pressure	0·444	0·518	0·739	0·847	1·004	1·180

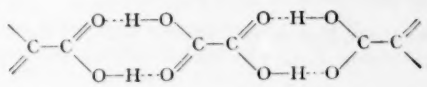
All attempts to measure the equilibrium pressure of water vapour in the system α-anhydrous acid–dihydrate–water vapour failed, apparently because the dihydrate gives the β-form on dehydration. The situation is similar to that in the system sodium sulphate hydrate–anhydrous sodium sulphate (which exists in a number of forms)–water vapour, for which we have not seen any statement of the form which is produced on dehydration of the hydrate.

The β-form has the lower lattice energy and might be expected to have the lower surface energy and be the form which would appear from the vapour according to nucleation theory. This is in fact the case; in the dehydration of the dihydrate interfacial energies must be considered, but a similar argument may apply. The appearance of the α-form from solution may be related to solvation effects or to the effects of adventitious particulate impurities.

Discussion on Lattice Energy of the Two Forms of Oxalic Acid.—The α-form of anhydrous oxalic acid contains molecular sheets, whereas in the β-form the molecules are arranged in chains, represented diagrammatically thus:



α



β

In both forms there are two hydrogen bonds per molecule (apart from end effects), so there is a considerable "background" contribution to the lattice energy in addition to the hydrogen-bonding energy; the latter may be assumed to be *ca.* 8 kcal. per bond (cf. Part I, *loc. cit.*). The differences in energy between the two structures are small; the entropy difference is rather larger than might be expected from the packing in the two forms, and may be associated with the restricted rotation about the C–C axis of the eight-membered ring of the β-form, which has the higher entropy (lower entropy of sublimation), whereas in the α-form this rotation is suppressed. At sufficiently high temperatures it is possible that the rotation becomes free, as might be revealed by specific-heat studies.

Section (b). Tetragonal Pentaerythritol.—Experimental. The pentaerythritol used had been purified by hydrolysis of the dibenzylidene compound. It was recrystallised from water and had m. p. 256°. The thermostat used in Section (*a*) was replaced by a double-walled vapour jacket, and temperatures were read on an Anschütz thermometer hanging near the effusion vessel. It was shown that the error in the thermometer due to expansion of the glass *in vacuo* was negligible. The rate of effusion was studied over the range 106·4—135·1° by the use of toluene, *n*-butyl alcohol, *iso*butyl alcohol, and chlorobenzene as boiling liquids. The same precautions were taken as in Section (*a*) to reduce errors. The results (Table 3) are well

TABLE 3. *Vapour pressures (cm. Hg) of tetragonal pentaerythritol.*

	Euffsion vessel 3					Effusion vessel 4				
T	106·40°	109·90°	110·15°	116·25°	119·20°	114·90°	119·15°	121·15°	128·50°	135·10°
V. p. × 10^5	2·12	3·34	3·48	6·97	9·84	5·84	9·45	12·40	28·1	52·4

represented by the equation $\log_{10} p_{\text{cm. Hg}} = 15{\cdot}17 - 7528/T$. The lattice energy is 34,400 cal. mole^{-1}, and the entropy of sublimation 60·8 cal. degree^{-1} mole^{-1}. These values differ considerably from those of Nitta, Seki, and Suzuki (*Bull. Chem. Soc. Japan*, 1951, **24**, 63), who carried out measurements at 124—137° and give $\log_{10} p_{\text{cm. Hg}} = 13{,}525 - 6861/T$, lattice energy 31,400 cal. mole^{-1}.

Discussion on Lattice Energy of Tetragonal Pentaerythritol.—In this form of pentaerythritol the molecules are linked by hydrogen bonds in sheets (Cox *et al.*, *loc. cit.*), with four hydrogen bonds per molecule. If we accept approximately 6 kcal. for the hydrogen-bond energy in alcohols, with the reservations mentioned in Part I (*loc. cit.*) (see Searcy, *J. Chem. Phys.*, 1949, **17**, 210), approximately 10 kcal. remain in the lattice energy owing to "background" interactions.

Nitta *et al.* (*loc. cit.*) attempted an analysis of the lattice energy of pentaerythritol, using the Slater–Kirkwood approximation for the dispersion energy, and splitting up the molecular interactions into those between groups (OH and CH_2). The electrostatic energy is calculated by the point charge method, but considerable difficulty arises in the assignment of residual charges to the atoms, and the values for the calculated lattice energy range

from 28·59 to 32·12 kcal. mole^{-1} according to the assignment of 36—42% ionic character to the hydrogen bond. The contribution to the electrostatic energy of next nearest neighbours is considerable. The calculation is provisional and may be criticised on the grounds that the energy of repulsion, higher (quadrupole) terms in the dispersion energy, and any small " resonance " contribution to the O–H–O bond energy are neglected. The dangers of neglecting the repulsion energy are revealed by Searcy's calculation for ice (see Part I, preceding paper). The calculation of Nitta *et al.*, with its summation of electrostatic interactions and dispersive interactions over the whole crystal, brings out the difficulty of defining the hydrogen-bond energy, a quantity which may in fact be dispensed with in the calculation of lattice energies, although the hydrogen bond provides a useful description of the shortening of O–O distances.

We thank Monsanto Chemicals Ltd. and the University of Leeds for grants to one of us (S. C.), and Professor E. G. Cox for his interest and encouragement.

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348. *The Vapour Pressure and Lattice Energy of Hydrogen-bonded Crystals. Part III.* 2-Thenoic, 2-Furoic, and Pyrrole-2-carboxylic Acids.*

By R. S. BRADLEY and A. D. CARE.

The vapour pressures of these three acids (thiophen-, furan-, and pyrrole-2-carboxylic acids) have been determined by a Knudsen effusion method over the respective temperature ranges 41·8—50°, 44—55°, and 76·6—80·4°. The lattice energies are respectively 23·17, 25·92, and 30·31 kcal. mole^{-1}, and the entropies of vaporisation 48·71, 58·28, and 62·76 cal. degree^{-1} mole^{-1}.

THE three acids mentioned in the title differ only in the presence in the ring of S, O, and NH respectively, and a comparison of the structures and thermodynamic properties is therefore of interest. The structure of 2-thenoic acid has been studied by Care and Cox and will be reported elsewhere.

EXPERIMENTAL

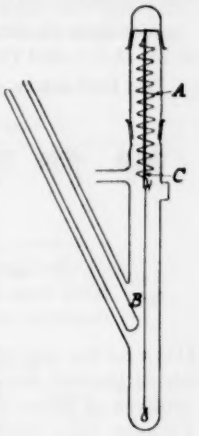
Preparation and Purification of Materials.—(a) *2-Thenoic acid.* The preparation was based on that of Voermann (*Rev. Trav. chim.*, 1907, **26**, 297). Thiophen was acetylated and sodium permanganate was added slowly, with stirring, to a mixture of acetylthiophen and aqueous sodium hydroxide. The solution was kept overnight and then heated on a water-bath until brown hydrated manganese dioxide was precipitated; this was filtered off, and dilute hydrochloric acid added to the filtrate until the solution was feebly alkaline. The filtrate was cooled, hydrogen peroxide added, and after a few hours' standing the solution was heated and stirred for a few minutes on a water-bath. 2-Thenoic acid was then precipitated by addition of hydrochloric acid, and the remainder was extracted from the solution by means of ether. The resulting brown crystals were recrystallised first from ethyl alcohol (charcoal) and then from hot water to give colourless needles, m. p. 126—127°, d_4^{18} 1·42 (from flotation in aqueous sulphuric acid).

(b) *2-Furoic acid.* This was obtained commercially and purified by sublimation; d_4^{18} 1·47.

(c) *Pyrrole-2-carboxylic acid.* McKay and Schmidt's method (*J. Amer. Chem. Soc.*, 1926, **48**, 192) gave only a poor yield, so the following method was devised. To ethylmagnesium iodide (from magnesium, 8·5 g.; ethyl iodide, 33 ml.; dry ether, 80 ml.), freshly distilled pyrrole (3·5 ml.) was added dropwise, with stirring, the container being cooled by ammonium nitrate, ice, and water to which solid carbon dioxide was added occasionally. The resulting solution was poured into a thick suspension of solid carbon dioxide in ether (*ca.* 1 l.) contained in a 2-l. flask. The contents of the flask set into a semi-solid mass and when all the carbon dioxide had evaporated the solid residue was separated from the ether, and the magnesium

* Part II, preceding paper.

salt decomposed by dilute hydrochloric acid. White crystals slowly settled on standing. These were separated and the solution was extracted with ether. The crystals became grey in air and were purified by treatment in hot ether with charcoal, filtration, and evaporation of the ether. The product was kept in a sealed tube in the dark; m. p. 191—191·5° (decomp.) (Found: C, 53·65; H, 4·5. Calc. for $C_5H_5O_2N$: C, 54·0; H, 4·5%), d_4^{18} 1·30.



Determination of Vapour Pressures.—The vapour pressures were determined by Knudsen's method, *i.e.*, measurement of the rate of effusion of vapour through a small hole in the wall of a bulb containing the solid. The effusion vessel (Bradley and Waghorn, *Proc. Roy. Soc.*, 1950, *A*, **206**, 65; Bradley and Shellard, *ibid.*, 1949, *A*, **198**, 239) consisted of a soft-glass bulb with a platinum-foil window which was pierced by a hole of the order of 0·5 mm. in diameter The rate of loss of vapour was followed by a McBain–Bakr balance, in a manner similar to that of Hopke and Sears (*J. Chem. Phys.*, 1951, **19**, 1345) and others, except that a fused-silica helical spring was used. The apparatus is shown in the Figure. The helical spring *A* had a sensitivity of (1—2·5) $\times$ 10^{-3} g. $mm.^{-1}$, and was calibrated for the load appropriate to the vapour-pressure experiments by means of small weights which were weighed on a Kuhlmann micro-analytical balance. The calibration plot of load versus extension was linear. Extensions could be read to 0·001 mm. Vapour effusing from the bulb under conditions of high vacuum was condensed on the surface *B*, which was cooled by means of acetone–solid carbon dioxide. Vibrational difficulties were avoided by the use of a *thick* rod *C* terminating in the reference pointer, by supporting the oil-pump on rubber mats and by making the connection to the apparatus by thick pressure-tubing. The temperature of the balance case was controlled by thermostat to $\pm$0·03°. Benzophenone, recrystallised from alcohol, was used as a calibrating substance.

Precautions were taken to reduce errors as described in Parts I and II (preceding papers). One defect of the method is that only a small range of temperature is available, since too high a temperature causes self-cooling and too low a temperature gives rates which are too small for study with a silica spring. The micro-balance method used in Parts I and II allows the study of a wider range of temperature, but involves more difficult experimentation.

Results.—2-*Thenoic* (α-*thiophenic or thiophen*-2-*carboxylic*) *acid.*

T	41·82°	41·93°	42·79°	45·15°	46·82°	50·02°
V. p. (cm. of Hg) $\times$ 10^5	27·9	28·8	31·6	40·5	49·9	72·3

Whence $\log_{10} p = -5065/T + 12{\cdot}53$; lattice energy = 23,170 cal. $mole^{-1}$; entropy of vaporisation = 48·71 cal. $degree^{-1}$ $mole^{-1}$.

2-*Furoic* (*furan*-2-*carboxylic*) *acid.*

T	44·06°	46·70°	49·65°	53·13°	55·05°
V. p. (cm. of Hg) $\times$ 10^5	62·3	80·4	115·8	178·3	227·2

Whence $\log_{10} p = -5667/T + 14{\cdot}62$; lattice energy = 25,920 cal. $mole^{-1}$; entropy of vaporisation = 58·28 cal. $degree^{-1}$ $mole^{-1}$.

Pyrrole-2-*carboxylic* (α-*pyrrolic*) *acid.*

T	76·58°	78·52°	79·08°	80·42°	81·97°	83·44°	85·61°
V. p. (cm. of Hg) $\times$ 10^5	42·68	54·0	58·1	68·7	81·7	98·5	127·2

Whence $\log_{10} p = -6633/T + 15{\cdot}60$; lattice energy = 30,310 cal. $mole^{-1}$; entropy of vaporisation = 62·76 cal. $degree^{-1}$ $mole^{-1}$.

In 2-thenoic acid there is one hydrogen bond per molecule, since the molecules are arranged in a helix with the carbonyl group of one molecule linked to the hydroxyl group of the next (Care and Cox, to be published). This implies that the contribution to the lattice energy of intermolecular forces, that of the hydrogen bond being omitted, is approx. 16 kcal. $mole^{-1}$, a value much greater than the latent heat of vaporisation of liquid thiophen (8·2 kcal. $mole^{-1}$) or methylthiophen (8·6 kcal. $mole^{-1}$). This is presumably due to the attraction between the carboxyl group of one molecule and the ring of another, and possibly to inductive effects of the carboxyl group on the ring (which will affect the action of one ring on another). A similar comparison can be made between benzene

(latent heat of sublimation 10 kcal. mole^{-1}) and benzoic acid (lattice energy 21 kcal. mole^{-1}). The structures of the remaining acids have not been calculated in detail, although pyrrole-2-carboxylic and 2-thenoic acids have the same space-group. It is hoped to publish a more detailed analysis when the structures have been established in detail.

We thank the Monsanto Chemical Co. Ltd. and the University of Leeds for grants to one of us (A. D. C.), and Professor E. G. Cox for his interest and encouragement.

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349. *The Vapour Pressure and Lattice Energy of Some Aromatic Ring Compounds.*

By R. S. BRADLEY and T. G. CLEASBY.

The vapour pressures, lattice energies, and entropies of vaporisation have been determined for naphthalene, anthracene, phenanthrene, fluorene, diphenyl, and pyrene by an effusion method.

DATA on the vapour pressures and lattice energies of the polycyclic aromatic hydrocarbons are in general discrepant or scanty. The lattice energies are of interest in view of the problem of interaction of conjugated systems which has been studied by de Boer (*Trans. Faraday Soc.*, 1936, **32**, 10), by Seki and Chihara (*Coll. Papers Fac. Sci. Osaka Univ.*, Series C, Chemistry, 1943—49, **11**, 1), and more recently by Coulson and Davies (*Trans. Faraday Soc.*, 1952, **48**, 777).

EXPERIMENTAL

The vapour pressures were considerably higher than those studied by the authors in their work on hydrogen-bonded crystals (*J.*, 1953, 1681), and it was not necessary to use a sensitive balance. A silica helical balance of the McBain–Bakr type was used to determine the rate of effusion of vapour from a small vessel, a cold finger cooled by acetone and solid carbon dioxide being used to condense the vapour. The apparatus was similar to that used by Bradley and Care (preceding paper): it was placed in a thermostat at the required temperature and, after assembly, was evacuated down to 1 mm. and left for 30 min. The pressure was then reduced to 10^{-5} cm., the cooling agent was added, and deflection–time readings were taken. Errors due to incorrect ratio of effusion hole size to mean free path, self-cooling, and radiation cooling were shown to be negligible. Benzophenone was used to calibrate the effusion vessels. Hydrocarbons were purified by recrystallisation from solution and by vacuum sublimation. The constants of the vapour-pressure equation and the entropies of vaporisation and lattice energies are given for all the compounds studied in Table 8, the equation being written as $\log_{10} p_{\text{cm. Hg}} = -A/T + B$. In no case was a curvature observable in the plot of log p against $1/T$.

Results for naphthalene are given in Table 1. Values given in the literature are surprisingly discrepant, as is seen from Table 2.

TABLE 1. *Vapour pressures* (*cm.* Hg) *of naphthalene.*

	Effusion vessel 1.								Effusion vessel 2.		
T	20·70°	18·70°	17·55°	17·35°	15·65°	13·85°	12·30°	8·10°	16·85°	12·70°	6·70°
V. p. × 10^3 ...	5·34	4·38	3·83	3·82	3·20	2·63	2·22	1·41	3·50	2·35	1·22

TABLE 2. *Comparison of published vapour pressures* (× 10^3; *cm.* Hg) *of naphthalene.*

Ref.	0°	5°	10°	15°	20°	Lattice energy (cal. mole^{-1})	Ref.	0°	5°	10°	15°	20°	Lattice energy (cal. mole^{-1})
1	0·708	1·17	1·95	3·16	5·13	15,700	5	0·6	1·0	2·1	3·5	5·4	17,900
2	0·430	—	1·30	—	4·10	17,900	6	2·3	—	—	—	6·4	8,000
3	—	—	1·74	—	6·48	19,600	7	—	—	1·54	—	6·4	—
4	2·2	3·4	4·7	6·2	8·0	11,000	8	—	0·993	1·73	2·96	4·92	17,300

References.—(1) Zilbermann-Granovskaya, *J. Phys. Chem. U.S.S.R.*, 1940, **14**, 759; calculated from $\log_{10} p = 9{\cdot}40 - 3429/T$. (2) Andrews, *J. Phys. Chem.*, 1926, **30**, 1497. (3) Swan and Mask, *J. Amer. Chem. Soc.*, 1925, **47**, 2112. (4) Allen, *J.*, 1900, **77**, 400. (5) Schlumberger, *J. Gasbeleuchtung*, 1912, **55**, 1257. (6) Barker, *Z. physikal. Chem.*, 1910, **71**, 235. (7) Sears and Hopke, *J. Amer. Chem. Soc.*, 1949, **71**. 1632. (8) This paper.

Sears and Hopke represent their result by an Antoine equation and consider that there is an unusual curvature in the plot of log p against $1/T$ in the region of 20°. We have not detected this curvature in our results over the range 6·7—20·7°, which show that the variation of lattice energy with temperature is negligible over this range.

Results for anthracene, phenanthrene, fluorene, diphenyl, and pyrene are given in Tables 3—7, respectively. Our results for anthracene agree with those of Sears and Hopke (*loc. cit.*) within ±3%.

TABLE 3. *Vapour pressures (cm. Hg) of anthracene.*

	Effusion vessel 3.					Effusion vessel 4.				
T	79·95°	77·25°	73·55°	69·91°	65·7°	80·40°	72·20°	71·25°	68·75°	67·10°
V. p. × 10^4	3·67	2·81	1·94	1·25	0·86	3·93	1·67	1·56	1·18	1·05

TABLE 4. *Vapour pressures (cm. Hg) of phenanthrene.*

	Effusion vessel 5.						Effusion vessel 6.				
T	48·80°	48·80°	46·70°	42·60°	39·85°	36·70°	49·65°	46·70°	44·62°	42·10°	39·15°
V. p. × 10^4	2·25	2·23	1·85	1·20	0·89	0·64	2·41	1·82	1·45	1·11	0·81

TABLE 5. *Vapour pressures (cm. Hg) of fluorene.*

	Effusion vessel 7.					Effusion vessel 8.				
T	49·25°	45·00°	40·30°	37·20°	33·30°	49·55°	47·75°	42·45°	38·45°	34·85°
V. p. × 10^4	8·18	5·43	3·43	2·50	1·64	8·33	7·08	4·16	2·81	1·95

TABLE 6. *Vapour pressures (cm. Hg) of diphenyl.*

	Effusion vessel 9.			Effusion vessel 10.					Effusion vessel 11.			
T	24·70°	20·70°	15·05°	40·55°	37·90°	35·10°	35·05°	32·45°	35·90°	31·25°	26·50°	23·05°
V. p. × 10^3	0·919	0·584	0·312	5·02	3·87	2·91	2·90	2·23	3·10	1·91	1·15	0·77
T				29·15°	27·05°	24·10°	24·00°					
V. p. × 10^3				1·54	1·20	0·888	0·887					

TABLE 7. *Vapour pressures (cm. Hg) of pyrene.*

	Effusion vessel 12.							Effusion vessel 13.				
T	85·00°	82·65°	81·70°	78·20°	78·05°	74·15°	68·90°	85·25°	82·70°	78·90°	75·85°	71·75°
V. p. × 10^4	3·79	3·07	2·92	2·06	1·97	1·41	0·86	3·80	3·04	2·16	1·67	1·08

TABLE 8. *Summary of vapour-pressure data.*

Hydrocarbon	Range of temp.	A	B	Lattice energy, cal. mole^{-1}	Entropy of vaporisation, cal. degree^{-1} mole^{-1}
Naphthalene	6·70—20·70°	3783	10·597	17,300	40·0
Anthracene	65·70—80·40	5320	11·638	24,400	44·7
Phenanthrene	36·70—49·65	4519	10·388	20,700	38·9
Fluorene	33·30—49·55	4324	10·325	19,800	39·1
Diphenyl	15·05—40·55	4262	11·282	19,500	43·0
Pyrene	71·75—85·25	4904	10·270	22,500	38·4

DISCUSSION

The lattice energy of benzene and of these hydrocarbons should be made up of two terms only, quantum-mechanical dispersion energy and energy of repulsion. The first approximation to the former, the molecule being taken as a whole and allowance made for the anisotropy of polarisability, gives for benzene far too small a result. In the next approximation the molecules are imagined to interact in units in the manner envisaged by de Boer (*loc. cit.*), who obtained good agreement with the experimental lattice energy of benzene, following the crystal-structure determined by Cox (*Proc. Roy. Soc.*, 1932, **135**, *A*, 491), and by using the Slater–Kirkwood approximation to the dispersion energy. However, energy of repulsion and higher terms in the dispersion energy have been neglected, and as London has pointed out, these conjugated systems give rise to induced dipoles in which the separation between positive and negative charges is large. His suggestion that the interaction should be studied in terms of monopoles does not lend itself readily to calculation. Coulson and Davies (*loc. cit.*) have therefore begun a study of intermolecular forces in conjugated chain compounds based on molecular-orbital theory. It would be

of interest if the packing of the zig-zag type for benzene could be shown to have the lowest energy, and if the angle of the plane of the rings to the axis could be determined theoretically. It would also be of interest to relate the lattice energy to the virial coefficient of the vapour, which has recently been determined accurately (Allen, Everett, and Penny, *Proc. Roy. Soc.*, 1952, *A*, **212**, 149; Casado, Massie, and Whytlaw-Gray, *ibid.*, *A*, **207**, 483).

For the three similar compounds, benzene, naphthalene, and anthracene, it is remarkable that the lattice energy per carbon atom is very nearly the same (1·78, 1·73, and 1·74 kcal., respectively). Phenanthrene and pyrene are less symmetrical and do not fit into this series. The lattice energies of diphenyl and of fluorene are nearly the same, as might be expected from the molecular form, but the entropy of vaporisation of the former is 43·0 as against 39·1 cal. degree^{-1} mole^{-1} for the latter, in agreement with the possibility of rotation about the central "single" bond for diphenyl in the vapour phase. The entropy of vaporisation of anthracene and the heat of vaporisation are greater than the corresponding quantities for the isomeric phenanthrene, in agreement with the closer packing and more symmetrical structure of the former (densities, anthracene 1·25, phenanthrene 0·98 at room temperature).

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350. *Tracer Studies in the Aquation and Hydrolysis of Cobalt Complexes.*

By C. A. BUNTON and D. R. LLEWELLYN.

Heavy oxygen being used as an isotopic tracer, it has been shown that in the hydrolysis of *C*-substituted acetatopentamminocobalt(III) ions $[R{\cdot}CO_2{\cdot}Co(NH_3)_5]^{++}$ there is a gradual change of the position of bond fission in the series $R = CH_3$, CH_2Cl, CCl_3, CF_3 from the Co–O bond with the weakly acidic acetic acid ligand to the C–O bond with the strongly acidic trifluoroacetic acid ligand. In aquation of acetato- and of trifluoroacetato-pentamminocobalt(III) ions there is no evidence for the breaking of the C–O bond. Evidence is put forward to suggest that the aquation of carbonatopentamminocobalt(III) nitrate may be regarded as a decarboxylation giving two products of normal abundance.

IN an investigation of the mechanism of substitution reactions in complex ions, Basolo, Bergmann, and Pearson (*J. Phys. Chem.*, 1952, **56**, 22) made a kinetic study of the hydrolysis and aquation of two series of *C*-substituted acetatopentamminocobalt(III) ions, one containing carboxylate groups of different base strength, and the other containing carboxylate groups of analogous base strength but of different size. The rates were found to parallel the base strength of the co-ordinated ligand but not its size, and these electronic and steric effects were taken as evidence that the substitution occurred either by an ionization mechanism or by a mechanism of the S_N2 type. As in certain cases it was found that the rate of hydrolysis was of second order, indicating a bimolecular mechanism, it was suggested that both hydrolysis and aquation involved nucleophilic substitution at the cobalt atom, with the entering groups approaching from the opposite side to the displaced carboxyl group.

This reasoning, however, gives no proof of the point of bond fission in either hydrolysis or aquation. In the aquation of carbonatopentamminocobalt(III) nitrate, Hunt, Rutenberg, and Taube (*J. Amer. Chem. Soc.*, 1952, **74**, 268) have shown by tracer studies that the Co–O bond is not broken, and suggest by analogy that similar bond fission may also occur in replacement reactions of carboxylatopentamminocobalt(III) complexes. It was decided to investigate the position of bond fission in hydrolysis and aquation of various carboxylatopentamminocobalt(III) complexes by ^{18}O tracer technique. For hydrolysis

the acetato-, and monochloro-, trichloro-, and trifluoro-acetato-, and for aquation, the acetato- and trifluoroacetato-complexes were studied. The reactions involved in hydrolysis and aquation may be written

$$[Co(NH_3)_5X]^{++} + OH^- \longrightarrow [Co(NH_3)_5OH]^{++} + X^-$$
$$[Co(NH_3)_5X]^{++} + H_2O \longrightarrow [Co(NH_3)_5,H_2O]^{+++} + X^-$$

It was not possible to follow the tracer in the substituting groups OH^- and H_2O because of the subsequent exchange of the ^{18}O in the hydroxy- or aquo-complex with the solvent, and it was decided to make the isotopic analysis on the carboxylic acid.

Two general methods of isolation of the carboxylic acid after reaction were used. In the first, the carboxylic acid was extracted with ether, from a slightly acid solution, and converted into the silver or sodium salt, which was decomposed to carbon dioxide by heating it *in vacuo* or in an atmosphere of bromine respectively. This general method was applied to the separation of the acid produced by hydrolysis of the acetato- and mono- and tri-chloroacetato-complexes and by the aquation of the acetato-complex.

In the second general method the hydroxy- or aquo-complex was removed from the reaction mixture by absorption on alumina, and the resulting neutral solution evaporated *in vacuo* and the dried sodium salt decomposed by bromine as before. This method was applied to the products of the hydrolysis of monochloro-, trichloro-, and trifluoro-acetato-complexes and the aquation of the last complex. It was found that the aquation of both acetato- and trifluoroacetato-complexes gave fission of the Co–O bond, and that hydrolysis of acetato- and mono- and tri-chloro-acetato-complexes gave completely or largely fission of the Co–O bond, but that hydrolysis of trifluoroacetato-complex gave fission of the C–O bond. In the aquation of carbonatopentamminocobalt(III) nitrate the isotopic composition of the carbon dioxide evolved was measured and found to be very nearly normal.

Experimental

The *C*-substituted acetatopentamminocobalt(III) nitrates were prepared according to the method of Basolo, Bergmann, and Pearson (*loc. cit.*) from the carbonatopentamminocobalt(III) nitrate (Werner and Gosling, *Ber.*, 1903, **36**, 2380; Lamb and Mysels, *J. Amer. Chem. Soc.*, 1945, **67**, 468) and analysed for ammonia by Horan and Eppig's method (*ibid.*, 1949, **71**, 581).

General Procedure for Hydrolysis.—A few hydrolyses were carried out under the conditions used by Basolo, Bergmann, and Pearson (*loc. cit.*) but in general the solutions used by these investigators were too dilute for convenient analysis and the following procedure was adopted.

Enriched water (20 ml.) was made 0·2N by addition of sodium hydroxide and 0·2M in the cobalt complex. The mixture was shaken until solution was complete and kept at 25° for 1—5 hr. depending on the nature of the complex.

Methods of Isolation.—Ether-extraction. The reaction mixture was filtered from any small precipitate of cobalt hydroxide, and brought to pH 1 by addition of nitric acid (5N), and the carboxylic acid extracted four times with ether. From each extraction the ether was run into sodium hydroxide solution (5N) to convert the free acid into the sodium salt in the aqueous layer. This separated aqueous layer was neutralised with nitric acid, barium chloride (50 mg.) added, and the solution filtered from any barium carbonate. The solution was evaporated to dryness *in vacuo*, and the residue warmed in bromine vapour. The permanent gas was pumped off at −180°, then the reaction mixture was allowed to warm to −80°, and the carbon dioxide examined by mass-spectrometer.

With the acetato-complex, silver nitrate was sometimes added to the neutralized reaction mixture at pH 5, and the precipitated silver acetate dried and decomposed by heat.

Alumina-extraction. The reaction mixture was filtered and allowed to percolate slowly through a dry column of alumina. The emerging liquid was a colourless neutral solution of the sodium salt of the carboxylic acid. Barium chloride (50 mg.) was added, and the solution filtered from carbonate. The solvent was distilled off *in vacuo*, and the residue treated with bromine as previously described.

These methods of extraction were checked by a number of experiments in which both normal and isotopically enriched samples of the acid were isolated under typical conditions.

General Procedure for Aquation.—Enriched water (20 ml.) was made 0·2M in the cobalt complex, brought to pH 4 by addition of nitric acid, and kept at 65° for 1—4 hr., depending on the nature of the complex. The reaction mixture was then brought to pH 1 and subjected to

the ether-extraction method of isolation, or made alkaline with sodium hydroxide, and the carboxylic acid isolated by the alumina method.

Results.—It was first shown that the methods of decomposition of the salts of the carboxylic acids to carbon dioxide gave carbon dioxide of an isotopic abundance sufficiently close to that of a sample of cylinder gas for the latter value to be used as a standard normal value of the isotopic composition in all our experiments. The values quoted for isotopic abundances of ^{18}O (Table 1) were determined by comparing the relative abundances of masses 44 and 46, *i.e.*, $^{12}C^{16}O^{16}O$ and $^{12}C^{16}O^{18}O$. The contribution to 46 by the species $^{13}C^{16}O^{17}O$ was ignored. If

TABLE 1. *Tests of isolation and decomposition methods.**

Acid		Abundance of ^{18}O in solvent H_2O, atoms-% excess	Method of isolation	Salt	Abundance of ^{18}O, atoms-% excess
Hydrolysis conditions.					
Enriched	$CH_3{\cdot}CO_2H$	Normal	Et_2O extn.	Ag *	0·465
			,,	Na	0·438
Enriched	$CH_2Cl{\cdot}CO_2H$	Normal	Direct	Na	0·703
		Normal	Al_2O_3	Na	0·738
Normal	$CH_2Cl{\cdot}CO_2H$	1·29	,,	Na	0·026
		1·29	,,	Na	0·036
		1·45	Et_2O extn.	Na	0·010
Enriched	$CCl_3{\cdot}CO_2H$	Normal	Direct	Na	1·298
		Normal	Et_2O extn.	Na	1·260
Enriched	$CCl_3{\cdot}CO_2OH$	Normal	Direct	Na	0·633
		Normal	Al_2O_3	Na	0·623
Enriched	$CCl_3{\cdot}CO_2H$	Normal	Direct	Na *	0·319
		Normal	Al_2O_3	Na	0·310
Normal	$CCl_3{\cdot}CO_2H$	1·45	Et_2O extn.	Na	0·032
		1·12	Al_2O_3	Na	0·030
		1·12	,,	Na	0·060
Enriched	$CF_3{\cdot}CO_2H$	Normal	Direct	Na	1·138
		Normal	Al_2O_3	Na	1·120
Normal	$CF_3{\cdot}CO_2H$	0·74	,,	Na	0·084
Aquation conditions.					
Normal	$CF_3{\cdot}CO_2H$	1·36	Direct	Na	0·315
		1·36	Al_2O_3	Na	0·278
		1·36	,,	Na	0·293

* The method of decomposition was by bromination, except that in the two cases thus marked it was by heat.

TABLE 2.

Complex	Abundance of ^{18}O in solvent H_2O, atom-% excess	Time of reaction, hours	Abundance of ^{18}O in CO_2H group	Atoms-% from water
	Hydrolysis results.			
$[Co(NH_3)_5,CH_3{\cdot}CO_2](NO_3)_2$	1·12	5	0·050	4
	1·12	5	0·038	3
	1·12	5	0·064	6
	1·12	5	0·021	2
$[Co(NH_3)_5,CH_2Cl{\cdot}CO_2](NO_3)_2$	1·45	3	0·09	6
	1·29	5	0·12	9
	0·97	3	0·07	7
$[Co(NH_3)_5,CCl_3{\cdot}CO_2](NO_3)_2$	1·450	1	0·167	12
	0·696	24 *	0·143	20
	0·696	6 *	0·170	24
	0·740	1	0·114	16
	0·740	1	0·087	13
$[Co(NH_3)_5,CF_3{\cdot}CO_2](NO_3)_2$	0·696	24 *	0·345	50
	0·696	6 *	0·321	46
	0·740	1	0·396	53
	0·740	1	0·422	57
	0·740	1	0·394	53
	0·740	1	0·413	56
	Aquation results.			
$[Co(NH_3)_5,CH_3{\cdot}CO_2](NO_3)_2$	1·53	4	0·065	4
	1·53	4	0·030	2
$[Co(NH_3)_5,CF_3{\cdot}CO_2](NO_3)_2$	1·36	2	0·393	—
	1·36	2	0·224	—

* Indicates reaction carried out under Basolo, Bergmann, and Pearson's kinetic conditions.

(abundance of mass 44)/(abundance of mass 46) = R, we have total atoms % of $^{18}O = 100/(2R + 1)$ = atoms-% excess + atoms-% in normal gas.

Tests of Isolation of Carboxylic Acids.—In these experiments the carboxylic acids of normal and enriched isotopic abundance were dissolved in water (normal and enriched) and kept under reaction conditions for an appropriate time. The acids were then isolated and decomposed to carbon dioxide by either of our general methods (see Tables 1 and 2).

Carbonato-aquation.—Carbonatopentamminocobalt(III) nitrate (0·1 g.) was dissolved in enriched water (5 c.c.) at 0° and degassed. Concentrated hydrochloric acid (3 drops) was added *in vacuo*, and after a few min. the mixture was cooled to −80° and the abundance of ^{18}O in the evolved carbon dioxide was measured (see following table). In the last experiment the reaction mixture was kept at room temperature for 40 min.

Abundance of ^{18}O in solvent H_2O, atoms % excess	1·36	1·36	1·36	1·36	1·36
Atoms, %, of ^{18}O in CO_2	0·021	0·075	0·022	0·052	0·136
Atoms, %, from H_2O	1·5	5	1·5	4	10

The methods of isolation and decomposition were also tested in a few cases by using enriched acids of known abundance.

Discussion

The tracer experiments in the aquation of acetato- and trifluoroacetato-pentamminocobalt(III) nitrate give no evidence for the breaking of the C–O bond The appreciable abundance of ^{18}O in the trifluoroacetic acid isolated from aquation is probably due to the extraneous oxygen exchange between this acid and water, which can occur, as shown by blank experiments, in the acidic solutions used for aquation.

It seems therefore that aquation of these carboxylato-complexes of cobalt(III) involves either an ionization mechanism or a bimolecular attack of a solvent molecule on the cobalt, *i.e.*, by S_N1 or S_N2 reactions, respectively. Neither the kinetic measurements of Basolo, Bergmann, and Pearson (*loc. cit.*) nor the tracer experiments reported here differentiate between these two possible mechanisms. The absence of acid catalysis under the conditions of the kinetic measurements as shown by Basolo, Bergmann, and Pearson indicates that the reacting entity is $[Co(NH_3)_5,R{\cdot}CO_2]^{++}$ and the reactions can be written as

$$(S_N1)\quad [Co(NH_3)_5,R{\cdot}CO_2]^{++} \longrightarrow [Co(NH_3)_5]^{+++} + R{\cdot}CO{\cdot}O^- \longrightarrow [Co(NH_3)_5,H_2O]^{+++}$$

$$(S_N2)\quad H_2O + [Co(NH_3)_5,R{\cdot}CO_2]^{++} \longrightarrow [(H_2O)Co(NH_3)_5]^{+++} + R{\cdot}CO{\cdot}O^-$$

In the hydrolysis of the carboxylato-complexes of pentamminocobalt(III) there appears to be a gradual change of the position of bond fission from the Co–O bond in the weakly acidic acetic acid ligand to the C–O bond in the strongly acid trifluoroacetic acid ligand. Both reactions are shown by their kinetic forms to be bimolecular and are therefore comparable to the S_N2 and $B_{AC}2$ mechanisms, respectively, of substitution and of ester hydrolysis (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37** 686; Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **166**, 679):

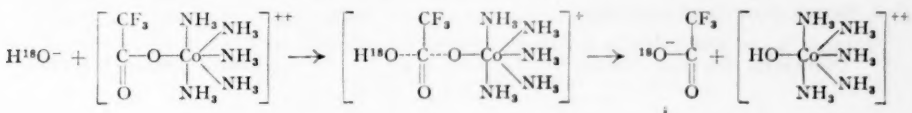
$$(S_N2)\quad {}^{18}OH^- + [Co(NH_3)_5{-}O{-}CO{\cdot}CH_3]^{++} \longrightarrow [H^{18}O{-}Co(NH_3)_5]^{++} + CH_3{\cdot}CO{\cdot}O^-$$

$$(B_{AC}2)\quad {}^{18}OH^- + [Co(NH_3)_5{-}O{-}CO{\cdot}CF_3]^{++} \longrightarrow [Co(NH_3)_5OH]^{++} + CF_3{\cdot}CO{\cdot}{}^{18}O^-$$

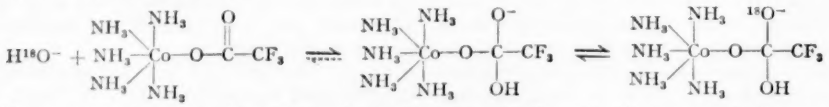
The $B_{AC}2$ mechanism is strongly favoured by electron withdrawal from the carbonyl-carbon atom, facilitating nucleophilic attack on this atom, and it is observable in the trichloroacetato-complex despite probable steric hindrance by the three chlorine atoms to attack on the carbonyl-carbon atom. In the hydrolysis of the trifluoroacetato-complex the very powerful electron withdrawal by the three fluorine atoms and the absence of steric hindrance makes the $B_{AC}2$ mechanism of prime importance.

It is not possible to ascertain from tracer experiments in their present form the precise amount of carbon–oxygen fission in any experiment.

If the $B_{AC}2$ mechanism involves a single-stage bimolecular substitution on the carbonyl-carbon atom, one of the two atoms of the isolated acid will be derived from the water, and the isotopic abundance of the acid will therefore be 50% of that of the water:



The mechanism may, however, involve the formation of a carbonyl-addition intermediate of finite life as observed in the hydrolysis of carboxylic esters (Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626) :



In this case some oxygen from the water will appear in the unhydrolysed cobalt complex, and the isotopic abundance of the isolated acid will therefore be more, by a small amount, than 50% of that of the water.

The uncertainty in our isotopic results owing to the small extraneous enrichment which occurs during isolation is such that we cannot differentiate between the two possibilities for the $B_{AC}2$ mechanism.

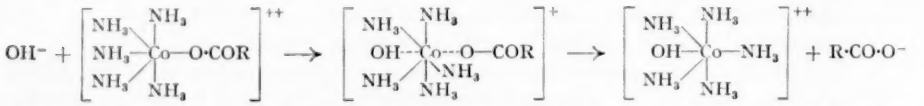
The tracer evidence for a change of bond fission, together with Basolo, Bergmann, and Pearson's kinetic measurements (*loc. cit.*), gives the following relative rate sequences for the two mechanisms :

Cobalt–oxygen bond fission, S_N2 : $CH_3{\cdot}CO_2 < CH_2Cl{\cdot}CO_2 < CCl_3{\cdot}CO_2 > CF_3{\cdot}CO_2$.

Carbon–oxygen bond fission, $B_{AC}2$: $CH_2Cl{\cdot}CO_2 < CCl_3{\cdot}CO_2 < CF_3{\cdot}CO_2$.

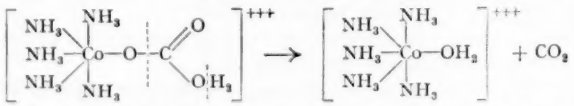
This rate sequence suggests an increased facility of attack on the cobalt on passage from acetato- to trichloroacetato-, with a marked decrease from trichloro- to trifluoro-acetato-; this decrease may be due to hydrogen bonding between the fluorine atoms and the hydrogen atoms of the ammino-groups. Such hydrogen bonding would inhibit nucleophilic attack on the cobalt atom. The electrostatic nature of the hydrogen bonding will probably increase the electron density on the cobalt atom and therefore inhibit the attack of hydroxide ion at this centre.

The hydrogen bonding could also make it more difficult for the five ammino-groups to take up their position in the transition state of the bimolecular displacement mechanism



Similar hydrogen bonding has already been suggested as a probable explanation of the formation of stable un-ionized addition compounds between trifluoroacetic acid and ethers and tertiary amines; this is in direct contrast to the inertness of acetic acid under similar conditions.

In the aquation of the carbonatopentamminocobalt(III) complex which reacts in solution as the bicarbonate complex (Lamb and Mysels, *J. Amer. Chem. Soc.*, 1945, **67**, 468) we find that the carbon dioxide evolved is of approximately normal isotopic abundance and that the small amount of tracer in the carbon dioxide is simply due to partial equilibration with the water. This evidence, taken in conjunction with Hunt, Rutenberg, and Taube's conclusion (*ibid.*, 1952, **74**, 268) that the cobalt–oxygen bond is not broken, a result which we have confirmed, shows that aquation of the carbonato-complex is a decarboxylation, rather than a hydrolysis giving two products of normal abundance :



The authors are indebted to Professor E. D. Hughes, F.R.S., for his initial suggestions on the problem and for his continued interest in this work and to Drs. P. B. D. de la Mare and C. A. Vernon for helpful discussion.

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351. *Griseofulvin. Part VII.* Dechlorogriseofulvin.*

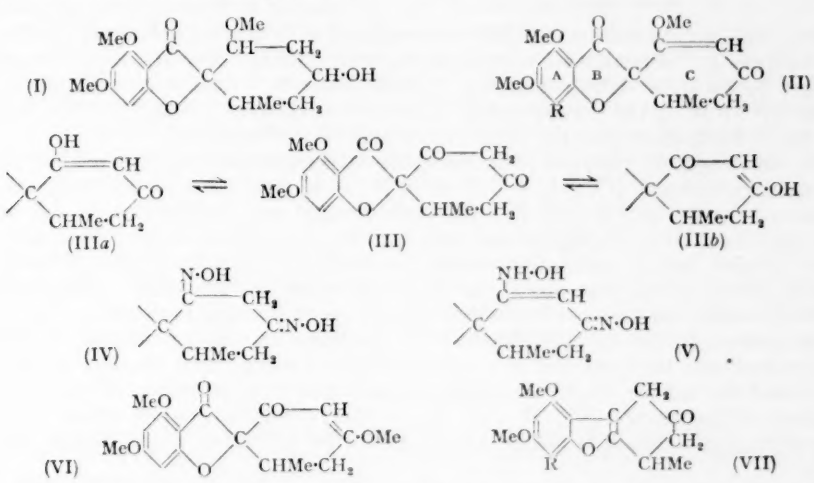
By J. MacMillan.

Dechlorogriseofulvin, $C_{17}H_{18}O_6$, the dechloro-derivative of griseofulvin, has been isolated from the culture filtrates of *Penicillium griseofulvum* Dierckx and certain strains of *Penicillium janczewskii* Zal. The chemistry of this new metabolite is described, together with a sensitive colour test for its detection in the presence of griseofulvin.

DECHLOROGRISEOFULVIN was isolated, together with griseofulvin, from the culture filtrates of *Penicillium griseofulvum* Dierckx and certain strains of *Penicillium janczewskii* Zal. [= *P. nigricans* (Bainier) Thom] (MacMillan, *Chem. and Ind.*, 1951, 719). Both species are known to produce griseofulvin (Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240; Brian, Curtis, and Hemming, *Trans. Brit. Mycol. Soc.*, 1946, **29**, 173; 1949, **32**, 30).

The fungi were grown and the culture filtrates extracted as described by Brian *et al.* (*loc. cit.*). Dechlorogriseofulvin and griseofulvin were isolated from the crude solid extract by chromatography on alumina or by fractional crystallisation from methanol or benzene. Dechlorogriseofulvin was obtained in yields of 30—50 mg. per l. from the culture filtrates of *P. griseofulvum* Dierckx, together with griseofulvin (60—100 mg. per l.), but several morphologically identical strains of *P. janczewskii* Zal., isolated from Wareham Heath soil, differed in their ability to produce dechlorogriseofulvin (see Experimental section). Although griseofulvin occurs both in the mycelium and culture filtrates of *P. griseofulvum* and *P. janczewskii*, dechlorogriseofulvin was isolated only from the culture filtrate.

Dechlorogriseofulvin, $C_{17}H_{18}O_6$, was shown to be the dechloro-analogue of griseofulvin by catalytic reduction to 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (I), obtained by reductive dechlorination of griseofulvin (Part V, *J.*, 1952, 3987). Dechlorogriseofulvin is therefore 4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (II; R = H) (cf. Part IV, *J.*, 1952, 3977). The ultra-violet and infra-red spectra closely resemble those of griseofulvin. The ultra-violet curve (see Figure) showed an expected small shift to shorter wave-length. The infra-red indicated the presence of two carbonyl groups, but only one of these was chemically reactive.

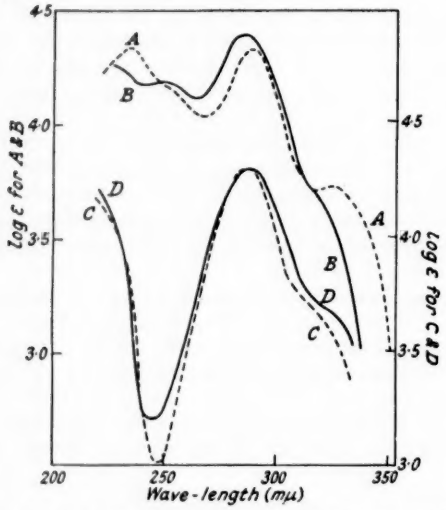


Like griseofulvin, dechlorogriseofulvin reacted with semicarbazide in pyridine and with methanolic ammonia to give basic derivatives (cf. Part I, *J.*, 1952, 3949).

* Part VI, *J.*, 1952, 3994.

Hydrolysis of dechlorogriseofulvin with dilute mineral acid gave the 1 : 3-diketone (IIIa $\rightleftharpoons$ III $\rightleftharpoons$ IIIb). With hydroxylamine at pH 5—6 this gave a derivative considered to be the dioxime (IV) rather than (V) since it was saturated to neutral permanganate. Methylation of (III) afforded dechlorogriseofulvin (II; R = H) and the isomeric (VI). Derivatives of all three tautomers of (III) have thus been prepared.

With 0·5N-sodium hydroxide, dechlorogriseofulvin yielded (III) and 1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (VII; R = H) whose structure and mode of formation were inferred by analogy with its counterpart (VII; R = Cl) in the griseofulvin series (cf. Part IV, *loc. cit.*). In this reaction, hydrolysis of one of the methoxyl groups in ring A did not take place; the only acidic product was (III). In this respect, dechlorogriseofulvin differs from griseofulvin; the lability of one of the aryl methoxyl groups in the latter towards alkali must be directly due to activation by the chloro-substituent.



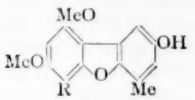
A, Griseofulvin in methanol.
B, Dechlorogriseofulvin in methanol.
2-Carbomethoxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, (C) in ethanol, and (D) in 0·1N-sodium hydroxide.

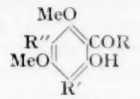
Both dechlorogriseofulvin and (III) were oxidised with alkaline yellow mercuric oxide to 3-hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran (VIII; R = H) which was also obtained by catalytic dehydrogenation of (VII; R = H). Catalytic dechlorination of the methyl ether of the corresponding griseofulvin oxidation product (VIII; R = Cl) (Part II, *J.*, 1952, 3958) gave the methyl ether of (VIII; R = H).

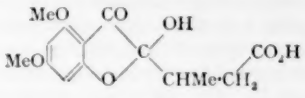
Zinc permanganate oxidation of dechlorogriseofulvin furnished the expected 2-hydroxy-4 : 6-dimethoxybenzoic (IX; R = OH, R′ = R″ = H) and 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (X), the latter isolated only as the lactone. A monobasic trimethoxy-acid, $C_{16}H_{18}O_8$, was also isolated, whose ultra-violet absorption (see Figure) showed that the coumaranone ring system was still present and that phenolic and enolic hydroxyl groups were absent (no shift in 0·1N-sodium hydroxide). The infra-red spectrum revealed the presence of a saturated ester group (band at 1740 cm.$^{-1}$); this group was hydrolysed by hot 3N-hydrochloric acid; methanol and carbon dioxide (1·3 moles) were evolved with the formation of a hygroscopic acid which could not be characterised but yielded the lactone of (X) on oxidation with zinc permanganate. These facts are consistent with structure (XI; R = H) for the third oxidation product whose formation from dechlorogriseofulvin is readily accounted for by oxidation at the double bond in ring C.

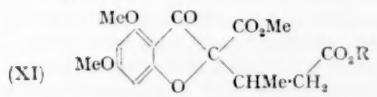
The infra-red spectrum of the acid (XI; R = H) in the solid state is noteworthy, showing only two bands in the double-bond stretching region (at 1740 and 1685 cm.$^{-1}$) and an OH band at 3120 cm.$^{-1}$. The frequency of the latter is much higher than that normally found in solid (dimeric) acids and suggests that (XI; R = H) exists in the solid as a

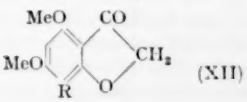
monomer with intra- or inter-molecular bonding between the hydroxyl group and the coumaranone-carbonyl group. On this basis, the band at 1685 cm.$^{-1}$ could be assigned to the coumaranone-carbonyl group and the fairly broad band at 1740 cm.$^{-1}$ could contain the ester- and carboxyl-carbonyl bands. In 0·12M-dioxan solution, (XI; R = H) showed carbonyl absorption bands at 1755, 1735, and 1715 cm.$^{-1}$. The band at 1735 cm.$^{-1}$ corresponds to the frequency found for saturated carboxylic acids in dioxan solution by Flett (*J.*, 1951, 962) and those at 1755 and 1715 cm.$^{-1}$ could be due to ester- and coumaranone-carbonyl respectively. In 0·02M-ethylene dichloride, only two carbonyl bands were distinguished (at 1755 and 1715 cm.$^{-1}$); the former could contain the ester- and


(VIII)


(IX)


(X)


(XI)


(XII)

carboxyl-carbonyl bands and the latter may be the coumaranone-carbonyl band. If these assignments are correct, the rise in frequency of the coumaranone-carbonyl band, from 1685 cm.$^{-1}$ in the solid to 1715 cm.$^{-1}$ in a non-polar solvent, indicates that it is inter-molecular bonding which takes place in the solid between the coumaranone-carbonyl and the hydroxyl group. The spectrum of the liquid methyl ester (XI; R = Me) possessed three carbonyl absorption bands—coumaranone-carbonyl at 1703 cm.$^{-1}$, and a very broad ester-carbonyl band at about 1740 cm.$^{-1}$ just resolvable into two maxima at about 1745 and 1735 cm.$^{-1}$.

As expected, the degradation products formed from ring C of griseofulvin were also obtained from dechlorogriseofulvin. Potassium hydroxide fusion and chromic oxide oxidation gave 5-methylresorcinol and 3-methoxy-2 : 5-toluquinone, respectively.

Dechlorogriseofulvin gives an intense blue-violet colour with nitric acid (*d* 1·42) at room temperature, whereas griseofulvin gives a pale yellow colour. This provides a sensitive test for dechlorogriseofulvin and can be used to disclose 1 μg. in a solid mixture. The colour is also produced in acetic acid solution but requires a large ratio of nitric to acetic acid. The violet colour was also given by the isomeric methyl ether (VI) and by the triketone (III) but not by the corresponding griseofulvin derivatives. That the reaction reflects the absence of the chloro-substituent in ring A was shown by the results obtained with a number of derivatives of phloroglucinol dimethyl ether. These results indicate that production of a violet colour with nitric acid may be diagnostic of the system (IX; R′ = R″ = H). For instance, the compounds (IX; R = OH, R′ = Cl, R″ = H; R = OH, R′ = H, R″ = Cl; R = OMe, R′ = Cl, R″ = H; and R = R″ = H, R′ = Me) and (XII; R = Cl) did not respond to the test whereas the corresponding compounds without the chloro- or methyl substituent did. Compounds without the COR grouping (phloroglucinol dimethyl ether, and the 2- and 4-chloro- and 2-methyl-derivatives) gave negative results. With phloroglucinol trimethyl ether derivatives corresponding to (IX; R′ = R″ = H), there was a colour shift to green.

Experimental

Some microanalyses were carried out by Mr. W. Brown of these laboratories.

In chromatography, B.D.H. alumina was rendered alkali-free (Prins and Shoppee, *J.*, 1946, 498) and activated for 3 hr. at 250°/17 mm.

4 : 6-Dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (III) was identified throughout by infra-red spectroscopy and its *X*-ray powder diagram.

Isolation of Dechlorogriseofulvin.—The crude material obtained by chloroform-extraction of the culture filtrates of *P. griseofulvum* and the dechlorogriseofulvin-producing strains of

P. janczewskii was provided by P. J. Curtis, C. H. Unwin, and G. L. F. Norris of these laboratories. The following are typical of many experiments.

(*a*) Crude solid extract (19·0 g.), from the culture filtrate of *P. janczewskii* (No. 571), in benzene (4 l.) was chromatographed on alumina (135 × 3·5 cm.). Development with ether–light petroleum (b. p. 40—60°) (1 : 1) gave a yellow band which was rapidly eluted and discarded. Continued development (3 days) afforded (i) a lower band fluorescing mauve in ultra-violet light, not completely separated from (ii) an upper broad band fluorescing blue. Elution of (i) yielded dechlorogriseofulvin (2·4 g.), m. p. 179—181°, after crystallisation from methanol. Band (ii) was eluted first with ether–light petroleum (b. p. 40—60°) (1 : 1) and then with benzene–ethanol (99 : 1), giving griseofulvin (8·1 g.), m. p. 218—220°, after several crystallisations from ethanol. The overlap between bands (i) and (ii) was fractionally eluted with the ether–light petroleum, giving fractions, m. p. 160—200° and 200—212°. Rechromatography of the former gave griseofulvin (710 mg.) and dechlorogriseofulvin (270 mg.); the latter yielded griseofulvin (1·5 g.), m. p. 212—216° after recrystallisation from ethanol.

Culture No. 250, the strain employed in earlier work in these laboratories on griseofulvin (Brian *et al.*, *loc. cit.*), produced no dechlorogriseofulvin. Cultures no. 571 and 573 afforded 15—30 mg. per l. of dechlorogriseofulvin together with griseofulvin (60—120 mg. per l.). Intermediate were cultures no. 963 and 964 from which only small amounts (3—5 mg. per l.) of dechlorogriseofulvin were obtained in addition to griseofulvin (60—100 mg. per l.).

(*b*) Crude solid extract (10·5 g.) from the culture filtrate of *P. griseofulvum* in benzene (2 l.) was freed from coloured contaminants by filtration through alumina (6 × 2·5 cm.). The broad colourless band fluorescing blue was eluted with benzene; the eluate and filtrate were concentrated stepwise, giving (i) griseofulvin (3·0 g.), m. p. 218—220° after several recrystallisations from ethanol, (ii) 4·15 g., m. p. 180—200°, (iii) 2·0 g., m. p. 169—174°, and (iv) 0·6 g., m. p. 170—180°. The combined fractions (iii) and (iv), after several crystallisations from methanol, afforded dechlorogriseofulvin in needles (1·9 g.), m. p. 179—181°.

Dechlorogriseofulvin crystallised from benzene or methanol in needles, m. p. 179—181°, raised to 180—210° on admixture with griseofulvin, $[\alpha]_D^{19}$ +390° (*c*, 1·0 in $COMe_2$) [Found: C, 64·4, 64·4, 64·2; H, 5·6, 5·4, 5·7; OMe, 27·0, 27·2%; *M* (Rast), 306. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7; 3OMe, 29·2%; *M*, 318]. Light absorption in MeOH: Max. ~325, 286, 250 (log ε 3·62, 4·39, 4·18).

Derivatives. The 2 : 4-*dinitrophenylhydrazone* formed red needles, decomp. 264—266° (from nitrobenzene–methanol) (Found: C, 55·5; H, 4·1; N, 11·15. $C_{23}H_{22}O_9N_4$ requires C, 55·4; H, 4·4; N, 11·15%).

With 1 mol., and also with excess, of hydroxylamine, only amorphous nitrogen-containing compounds were obtained.

Treatment with semicarbazide hydrochloride in pyridine for 2 days at room temperature followed by dilution gave the (?) *pyrazoline*, buff needles, decomp. 240—242° (from ethanol) (Found: C, 57·2; H, 5·7; N, 11·2; OMe, 28·2. $C_{18}H_{21}O_6N_3$ requires C, 57·6; H, 5·6; N, 11·2; 3OMe, 25·0%). It was basic and in ethanol gave a wine-red ferric chloride colour discharged on addition of water. The Knorr pyrazoline test was negative. Its mineral acid solutions slowly deposited an unsaturated, nitrogen-containing compound which gave 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione with warm mineral acid.

The *amine*, obtained as for griseofulvamine (Part I, *loc. cit.*), crystallised from aqueous methanol in needles, m. p. 198—200° (Found: C, 59·7; H, 5·9; N, 4·6; OMe, 21·4. $C_{16}H_{17}O_5N,H_2O$ requires C, 59·8; H, 5·9; N, 4·4; 2OMe, 19·3%). It was basic, gave the same ferric chloride colour reaction as the pyrazoline and was hydrolysed with warm mineral acid to 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione; it did not react with Brady's reagent. Its *monoacetyl* derivative crystallised from ethanol in needles, m. p. 247—249° (Found: C, 62·4; H, 5·4; N, 3·6. $C_{18}H_{19}O_6N$ requires C, 62·6; H, 5·5; N, 4·0%). The 2 : 4-*dinitrophenylhydrazone* of the acetyl derivative crystallised from nitrobenzene–methanol in red needles, decomp. 287—289° (Found: C, 54·9; H, 4·4; N, 13·5. $C_{24}H_{23}O_9N_5$ requires C, 54·9; H, 4·4; N, 13·3%).

4′-*Hydroxy*-4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3-*one* (I).—Dechlorogriseofulvin (200 mg.) in acetic acid (10 ml.) was hydrogenated in the presence of Adams's catalyst (100 mg.) (2 mols. absorbed in 1·5 hr.). Removal of the catalyst and solvent gave 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (120 mg.) (Part V, *loc. cit.*), m. p. 222° (corr.), identified by mixed m. p., analysis, and infra-red spectrum.

Hydrolysis of Dechlorogriseofulvin.—(a) *Acid.* The compound (1·3 g.) in methanol (200 ml.) was heated under reflux for 6 hr. with 2N-hydrochloric acid (250 ml.). Removal of the methanol

gave **4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione***, prisms (1·1 g.), decomp. 248—250° (from acetic acid), $[\alpha]_D^{21}$ +480° (*c*, 1·0; Na salt in H_2O) [Found: C, 63·2, 63·1; H, 5·3, 5·2; OMe, 20·1, 19·0%; equiv. (potentiometric), 290. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3; 2OMe, 20·4%; equiv., 304]. The ***dioxime***, prepared by heating the trione (320 mg.) under reflux with hydroxylamine hydrochloride (500 mg.) and 0·116N-sodium hydroxide (6·3 ml.), crystallised from 2-methoxyethanol in needles, decomp. 231—233° (Found: C, 57·25; H, 5·5; N, 8·5. $C_{16}H_{18}O_6N_2$ requires C, 57·5; H, 5·4; N, 8·4%).

(b) *Alkaline*. Dechlorogriseofulvin (1·3 g.) was heated under reflux for 5 hr. in nitrogen with 0·5N-sodium hydroxide. After complete dissolution (1 hr.), a yellow oil separated which solidified on cooling and was collected; it sublimed at 70—80°/10^{-4} mm., giving **1 : 2 : 3 : 4-*tetrahydro*-3-*keto*-5 : 7-*dimethoxy*-1-*methyldibenzofuran***, needles (230 mg.), m. p. 99—100° (from methanol), $[\alpha]_D^{21}$ −25° (*c*, 1·0 in $COMe_2$) (Found: C, 69·2, 68·9; H, 6·2, 6·2; OMe, 21·9. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2; 2OMe, 23·8%). Light absorption in EtOH: Max. 256, 216 mμ (log ε 4·14, 4·47). The ***dinitrophenylhydrazone*** crystallised in red needles (from nitrobenzene–methanol), decomp. 247—248° (Found: C, 57·1; H, 4·7; N, 12·9. $C_{21}H_{20}O_7N_4$ requires C, 57·3; H, 4·6; N, 12·7%).

The acidic fraction, recovered from the alkaline mother-liquors, was fractionally crystallised from acetic acid but the sole product was the trione (III) (600 mg.), decomp. 240—242°. The most soluble fraction was also identified by analysis [Found: C, 63·0; H, 5·4; OMe, 19·0%; equiv. (potentiometric), 300]. The reaction was less clean in air but gave similar results.

Methylation of **4 : 6-*Dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione***.—The acid (880 mg.), suspended in ether (100 ml.) and methanol (20 ml.), was treated overnight with excess of diazomethane, and the recovered gum was chromatographed on alumina (35 × 1·0 cm.) from its benzene solution. The lower broad band, fluorescing light blue in ultra-violet light, was eluted with benzene–ether (4 : 1), giving **4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione*** as a gum (270 mg.) which could only be obtained solid by adding its methanolic solution to a large volume of water (Found: C, 63·8; H, 5·9; OMe, 28·6. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7; 3OMe, 29·2%). Light absorption in EtOH: Max. ~323, 286, 266 mμ (log ε 3·7, 4·425, 4·424). The upper band, fluorescing blue, was eluted with benzene containing 1% of methanol, and gave dechlorogriseofulvin (305 mg.) which, after crystallisation from methanol, had m. p. and mixed m. p. 177—179°.

Oxidation of Dechlorogriseofulvin.—(a) *Chromic oxide*. The compound (250 mg.) in acetic acid (4 ml.) was treated dropwise with chromic oxide (750 mg.) in acetic acid (4 ml.) and water (1·5 ml.). After the vigorous reaction, induced by gentle warming, had subsided (10 min.), the mixture was heated under reflux for ½ hr. Dilution and extraction with benzene gave 3-methoxy-2 : 5-toluquinone, separated from starting material by sublimation at 95°/10^{-4} mm. and identified by mixed m. p. (147—148°) after crystallisation from methanol.

(b) *Mercuric oxide*. Dechlorogriseofulvin (1·6 g.), suspended in 0·67N-sodium hydroxide, was oxidised with yellow mercuric oxide (2·5 g.) and worked up as described for griseofulvin (Part II), giving **3-*hydroxy*-5 : 7-*dimethoxy*-1-*methyldibenzofuran***, needles (200 mg.), m. p. 169—171° (from benzene) (Found: C, 69·5, 69·7; H, 5·3, 5·2; OMe, 26·0. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4; 2OMe, 24·0%). Light absorption in MeOH: Max. 314, 285, 264, 230 mμ (log ε 4·02, 4·2, 4·24, 42·9); its ***picrate*** formed red needles, m. p. 155°, from benzene (Found: C, 51·9; H, 3·1; N, 8·65. $C_{15}H_{14}O_4,C_6H_3O_7N_3$ requires C, 51·8; H, 3·5; N, 8·6%). The phenol gave no ferric chloride colour reaction.

The ***methyl ether***, obtained with methyl sulphate and alkali, crystallised from methanol in prisms, m. p. 118° (Found: C, 71·0; H, 5·8; OMe, 32·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9; 3OMe, 34·2%). Light absorption in MeOH: Max. 311, 285, 264, 230 mμ (log ε 4·13, 4·29, 4·36, 4·66); it gave a ***picrate*** as red needles, m. p. 148—149°, from methanol (Found: C, 52·7; H, 3·8. $C_{16}H_{16}O_4,C_6H_3O_7N_3$ requires C, 52·7; H, 3·7%).

Oxidation of **4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione** (800 mg.) in the same way gave the dibenzofuran (250 mg.) and 300 mg. of recovered starting material.

(c) *Zinc permanganate*. Dechlorogriseofulvin (2·37 g.) in alcohol-free acetone (850 ml.) was treated slowly (¾ hr.) with 1% aqueous zinc permanganate (500 ml.). After 2 hr. at room temperature with occasional shaking, the manganese dioxide was filtered off, washed with acetone, and extracted with dilute aqueous ammonia. Acidification of the ammoniacal extract, extraction with ether, and recovery gave 2-hydroxy-4 : 6-dimethoxybenzoic acid (95 mg.), m. p. 157—159°, identical (mixed m. p.) with a synthetic specimen.

The aqueous-acetone mother-liquors and washings were concentrated to *ca.* 300 ml. and then extracted with ethyl acetate, and the ethyl acetate extract in turn was extracted with sodium

hydrogen carbonate. Recovery of the ethyl acetate layer gave the *lactone* of 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid as needles (275 mg.), m. p. 170—171° (from methanol or ethyl acetate–light petroleum), $[\alpha]_D^{18}$ −23·5° (*c*, 0·72 in $COMe_2$) (Found: C, 61·0, 60·9; H, 5·3, 5·1; OMe, 21·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1; 2OMe, 22·0%). It slowly dissolved in warm dilute sodium hydroxide and hydrogen carbonate to a yellow solution, acidification of which discharged the colour and gave a mixture of the lactone and the free acid.

The sodium hydrogen carbonate extract, on acidification and recovery, afforded a gum, trituration of which with benzene gave the *acid* (XI; R = H) as plates (220 mg.), m. p. 213—215°, from aqueous methanol (prisms from ethyl acetate) [Found: C, 56·9; H, 5·4; OMe, 27·5%; equiv. (potentiometric), 324. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3; 3OMe, 27·5%; equiv., 338]. Light absorption max.: in EtOH, ~323, 288, ~235 mμ (log ε 3·66, 4·3, 3·7), in 0·1N-NaOH, ~325, 288, ~230 mμ (log ε 3·66, 4·3, 3·97). Recovery of the benzene filtrate from the acid (XI; R = H) afforded a gum which was heated for 3 days at 35° with acetic anhydride (1 ml.) in pyridine (0·5 ml.). Dilution gave a solid which was separated by sodium hydrogen carbonate extraction into the above lactone (375 mg.) and the acid (XI; R = H) (88 mg.).

The *methyl* ester (XI; R = Me), obtained with diazomethane, distilled at 120° (bath-temp.)/10^{-4} mm. (Found: C, 58·1; H, 6·0; OMe, 33·2. $C_{17}H_{20}O_8$ requires C, 58·0; H, 5·7; 4OMe, 35·2%).

Conversion of 2-Carbomethoxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric Acid (XI; R = H) *into the Lactone of 2-Hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric Acid.*—The acid (XI; R = H) (100 mg.), heated under reflux in nitrogen with 3N-hydrochloric acid (baryta trap), dissolved in 1 hr. with liberation of 1·3 mols. of carbon dioxide and methanol (chromotropic acid test). Extraction of the cooled solution with ether and recovery gave a gummy hygroscopic acid (53 mg.) which was treated at 0° in N-sodium carbonate (5 ml.) with 1% zinc permanganate (9 ml., 4·5 atoms of O). Decolorisation with sulphur dioxide, addition of 3N-hydrochloric acid, and extraction with ether gave a gum. Treatment of the latter in pyridine with acetic anhydride for 3 days at 35°, dilution, and extraction with ethyl acetate afforded the lactone of 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, m. p. 166—168°, identified by mixed m. p. and infra-red spectrum.

Dehydrogenation of 1 : 2 : 3 : 4-Tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran.—The compound (100 mg.) in 2-methylnaphthalene (5 ml.) was heated under reflux in nitrogen for 6 hr. with 5% palladium–charcoal (100 mg.). After addition of ether, filtration, and removal of ether, water (10 ml.) and 3N-sodium hydroxide (1 ml.) were added and the 2-methylnaphthalene removed by steam-distillation. Acidification of the filtered alkaline solution gave 3-hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran (43 mg.), m. p. and mixed m. p. 170—171° (picrate, m. p. and mixed m. p. 156—157°).

Dechlorination of 8-Chloro-3 : 5 : 7-trimethoxy-1-methyldibenzofuran.—The compound (45 mg.) (Part II) in ethanol containing 10% ethanolic potassium hydroxide (2·5 ml.) was shaken in hydrogen for 6 hr. with 2% palladised strontium carbonate (300 mg.). The filtered solution was diluted with water and neutralised, and the ethanol removed at 40° *in vacuo*. Ether-extraction and recovery gave 3 : 5 : 7-trimethoxy-1-methyldibenzofuran (36 mg.), m. p. and mixed m. p. 118—119° (picrate, m. p. and mixed m. p. 148—149°).

Fusion of Dechlorogriseofulvin with Potassium Hydroxide.—Carried out as described for griseofulvin (Oxford *et al.*, *loc. cit.*), this gave 5-methylresorcinol (0·7 mol.).

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352. *N-Substituted Glycosylamines derived from Sulphanilamide and p-Aminosalicylic Acid.*

By R. Bognár and P. Nánási.

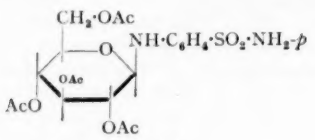
A number of *N*-arylglycosylamines derived from sulphanilamide and *p*-aminosalicylic acid, together with the methyl, ethyl, and *n*-propyl esters of the latter, have been synthesised and examined. Both the anomeric forms (I, II) of *N*-*p*-sulphamylphenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate have been prepared, and it has been shown that on deacetylation they give *N*-*p*-sulphamylphenyl-D-glucosylamine (III). Acetylation of (I), (II), or (III) gives the *NN'* : 2 : 3 : 4 : 6-hexa-acetate (IV). The preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate is described, a new method is given for the synthesis of 2 : 3 : 4 : 6-tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose, and its conversion into the hexa-acetate is reported. By interaction of 2 : 3 : 4 : 6-tetra-acetyl D-glucosylamine with *N*-acetylsulphanilyl chloride, *N*-*p*-acetamidobenzenesulphonyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (V) has been prepared. Ultraviolet absorption data for several *p*-aminosalicylic acid derivatives are included.

In 1938, because of the therapeutic effect of sulphanilamide, Kuhn and Birkofer (*Ber.*, 1938, **71**, 621) described *N*-*p*-sulphamylphenyl-D-glucosylamine, and later workers have prepared many analogous compounds (see E. H. Northey, "Sulfonamides and Allied Compounds," Reinhold Publ. Corp., New York, 1948). Although these glycosylated sulphonamides are not distinctly superior to the free sulphonamides in their effect (Lehr, Bloch, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1415) their greater solubility in water is of interest (*Chem. Abs.*, 1941, **35**, 6978). Despite their higher concentration in the blood certain *N*-*p*-sulphamylphenylglycosylamines are less toxic and better tolerated than the corresponding sulphanilamides (*Chem. Abs.*, 1940, **34**, 5857). Chemically, the chief interest lies in the possibilities of isomerism : in addition to displaying αβ-anomerism, which is theoretically possible in every glycosylamine, the sugar moiety may exist in the pyranose or furanose form ; further there are two nitrogen atoms in sulphanilamide at which glycosylation may take place, leading to, *e.g.*, (III) and (V). In *p*-aminosalicylic acid glycosylation is possible at the amino-, carboxyl, or hydroxyl group, giving respectively (VI), (VII), or (VIII).

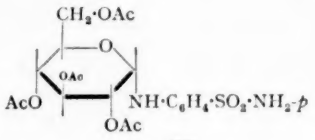
N-Arylglycosylamines were first prepared by Sorokin (*J. pr. Chem.*, 1888, **37**, 291) and since then many similar substances have been isolated. Initially it was doubtful whether these compounds were true glycosylamines or derivatives of the Schiff-base type, but later work favours the glycosylamine structure (concerning *N*-*p*-sulphamylphenylglycosylamine see Northey, *op. cit.*). Kuhn and Birkofer (*loc. cit.*) prepared the glucosylamine by direct condensation of glucose with sulphanilamide in 95% ethanol, using ammonium chloride as a catalyst. If the sugar is only slightly soluble in ethanol, as in our experiments with lactose and cellobiose, it was necessary to use Weygand's method (*Ber.*, 1940, **73**, 1259), which consists in fusing the reactants in the presence of a small quantity of dilute hydrochloric acid for a few minutes. *N*-Arylglycosylamines acetylated in the sugar residue have been prepared by Fischer and Helferich (*Ber.*, 1914, **47**, 2107), Sabalitschka (*Ber. deutsch. physikal. Ges.*, 1921, **31**, 439), J. W. Baker (*J.*, 1924, **125**, 268), and Butler, Smith, and Stacey (*J.*, 1949, 3371 and other papers) from acetobromo-sugars, by Frèrejacque (*Compt. rend.*, 1936, **202**, 1190; 1938, **207**, 638) from fully acetylated sugars, and by Weisz (Diss., Budapest, 1940), by Bognár (*Proc. Chem. Acad. Hungary*, 1951, I, **2**, 28), and by Butler *et al.* (*loc. cit.*) from partly acetylated sugars containing free glycosidic hydroxyl groups. All these syntheses involved condensation of the arylamino-nitrogen atom with the sugar residue but, while the present work was in progress, Helferich and Mitrowsky (*Ber.*, 1952, **85**, 1) reported the isolation of products formed by condensation of tetra-acetyl D-glycosylamine with arylsulphonyl chlorides, in which the sugar-nitrogen atom and

the sulphonyl group are linked together. A similar compound (V) is described in this paper and glycosylamino-acids are in course of preparation in this laboratory.

In the present researches, by means of Kuhn and Birkofer's technique crystalline *N*-*p*-sulphamylphenyl derivatives of L-arabinose, D-xylose, D-galactose, D-mannose, and maltose have been obtained. Similar crystalline derivatives of lactose and cellobiose have been isolated in good yield by the alternative method of Weygand (*loc. cit.*). *N*-*p*-Sulphamylphenyl-lactosylamine was found to be very soluble in water, and is being investigated pharmacologically.



(I)



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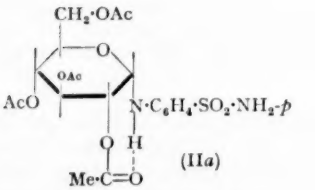
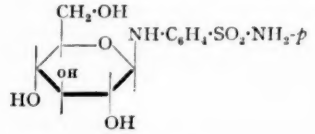
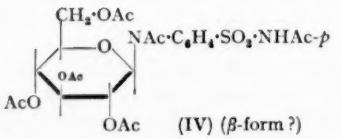


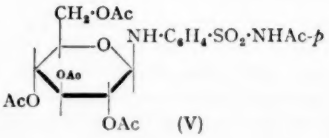
(IIa)



(III)



(IV) (β-form?)

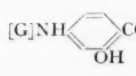


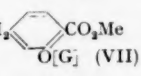
(V)

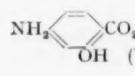
In addition to the unsubstituted *N*-*p*-sulphamylphenylglycosylamines, acetylated derivatives have been isolated by condensation of either acetobromoglucose (Braun *et al.*, *loc. cit.*) or 2 : 3 : 4 : 6-tetra-acetyl glucose with sulphanilamide. The latter method proved very suitable with hepta-acetyl cellobiose for the preparation of crystalline *N*-*p*-sulphamylphenylcellobiosylamine hepta-acetate. With acetobromoglucose a mixture of α- and β-anomers of *N*-*p*-sulphamylphenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate was obtained from which was isolated a pure crystalline β-form (I), m. p. 204°, $[\alpha]_D$ −81° in pyridine, identical with the compound synthesised by Braun *et al.* and by Kuhn and Birkofer (*locc. cit.*). Addition of water to the mother-liquors gave a substance rich in the α-form (II); this material, after repeated recrystallisation from ethanol, had m. p. 204—205°, $[\alpha]_D$ +203° in pyridine, +197° in $CHCl_3$. A similar mixture, containing, however, a higher proportion of the β-isomer, was obtained from tetra-acetyl glucose. It is considered that (I) and (II) are anomers, and not structural isomers arising from substitution of the sulphamido-nitrogen atom, since they contain no primary arylamine-nitrogen and since condensation between benzenesulphamide and acetobromoglucose cannot be effected. The Schiff-base structure is unlikely because of the mode of the formation of the acetylated substances and because *N*-*p*-sulphamylphenylglucosylamine is not reduced even at 50 atm. Deacetylation of mixtures containing different proportions of α- and β-anomers always gave rise to the known *N*-*p*-sulphamylphenyl-D-glucosylamine (III), m. p. 204°, $[\alpha]_D$ −117° in pyridine, presumed to be the β-form. With acetic anhydride and zinc chloride, the α- and β-tetra-acetyl compounds (I) and (II), and the unacetylated compound (III), gave the same hexa-acetyl *N*-*p*-sulphamylphenyl-D-glucosylamine (IV), m. p. 115°, $[\alpha]_D$ +77° in pyridine. Similar properties have been reported for the α- and β-isomers of *N*-phenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (Honeyman and Tatchell, *J.*, 1950, 967) and of *N*-phenyl-D-galactosylamine 2 : 3 : 4 : 6-tetra-acetate (Butler *et al.*, *loc. cit.*), which are

moderately stable and on deacetylation give single glycosylamines. Furthermore, a single penta-acetyl derivative was obtained by acetylation of either *N*-phenyl-α- or -β-D-glucosylamine tetra-acetate (Bognár, *loc. cit.*). It appears that in the unacetylated compound (III) and in the hexa-acetate (IV) only one isomer is stable whereas in the case of the tetra-acetate both anomers can be isolated and we consider it possible that the stabilisation of the α-form (II) is due to a type of hydrogen bonding (II*a*) similar to that tentatively suggested by Todd *et al.* (*J.*, 1946, 853) for acetylated *N*-glycosylamines. A comparable example of intramolecular hydrogen bonding in a seven-membered ring has been deduced from infra-red absorption measurements on acetylglycine *N*-methylamide by Mizushima *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 270).

When this work began, no sugar derivatives of *p*-aminosalicylic acid had been reported, but since then Sannié and Lapin (*Bull. Soc. chim.*, 1950, 1234) have reported the isolation of compounds analogous to (VI), (VII), and (VIII). They prepared *N*-(4-carboxy-3-


(VI)


(VII)


(VIII)

[G] = D-Glucopyranosyl.

hydroxyphenyl)-D-glucosylamine (VI) by a variation of Sorokin's method (*loc. cit.*) and assigned its structure by analogy with the *N*-*p*-carboxyphenylglycosylamines (Sannié *et al.*, *Compt. rend.*, 1948, **226**, 182; *Bull. Soc. chim.*, 1948, 892). Reduction and deacetylation of the product obtained by interaction of acetobromoglucose with sodium *p*-nitrosalicylate gave amorphous 1-(4-amino-2-hydroxybenzoyl)-D-glucose (VIII); and 5′-amino-2′-carbomethoxyphenyl-D-glucoside (VII) was obtained in a similar way from the sodium salt of methyl *p*-nitrosalicylate. In the present work a modification of Kuhn and Birkofer's method (see p. 1707) has been used for the preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine (VI), and of its methyl, ethyl, and propyl esters, and for the preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-galactosylamine. Weygand's method (*loc. cit.*) was unsuitable because, under the conditions used, some decarboxylation of *p*-aminosalicylic acid occurred. Acetylated derivatives were prepared by a modification of Frèrejacque's method (Bognár, *loc. cit.*). *p*-Aminosalicylic acid and 2 : 3 : 4 : 6-tetra-acetyl D-glucose gave *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate. All these *N*-arylglycosylamines gave typical reactions for a carboxyphenol and negative tests for a primary arylamine group. Although Sannié and Lapin (*loc. cit.*) were unable to condense acetobromoglucose directly with *p*-aminosalicylic acid, yet with these reagents in the presence of acetone and sodium hydroxide we obtained 2 : 3 : 4 : 6-tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose, which gave positive tests for the phenolic and primary arylamine groups and negative tests for the carboxyl residue. Acetylation of this compound gave 1-(4-acetamido-2-acetoxybenzoyl) 2 : 3 : 4 : 6-tetra-acetyl D-glucose, the ultra-violet absorption spectrum of which closely resembled that of 4-acetamido-2-acetoxybenzoic acid. Hydrolysis with sodium methoxide gave crystalline methyl *p*-aminosalicylate.

The ultra-violet absorption spectra of a number of these substances were examined. In the case of sulphanilamide, *N*-glycosylation of either nitrogen atom does not alter significantly the positions of the maxima. With *p*-aminosalicylic acid, however, appreciable differences are observed, although *N*-glycosylation has a less marked effect than *N*-acetylation.

Experimental

N-p-*Sulphamylphenylglycosylamines.*—Several of these glycosylamines were prepared by direct combination of sulphanilamide with the free sugar (Kuhn and Birkofer, *loc. cit.*). The sugar (1 mol.) was refluxed in 96% ethanol (10 vol.) with sulphanilamide (1 mol.) for 2—3 hr. The crude glycosylamines from D-glucose and D-mannose crystallised from the boiling solution; those from L-arabinose, D-xylose, and D-galactose crystallised on cooling. Removal of some of the ethanol was necessary to induce crystallisation of the maltose derivative. The glycosylamines from D-galactose, lactose, and cellobiose were synthesised by Weygand's method (*loc. cit.*): The finely powdered sugar (1 mol.), and sulphanilamide (1 mol.) were fused with a small quantity of 0·25N-hydrochloric acid on the steam-bath for a few min. The crude product was

recrystallised from aqueous ethanol. The properties of these compounds are summarised in Table 1.

N-p-*Sulphamylphenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—(*a*) Sulphanilamide (6·8 g., 1 mol.) and acetobromoglucose (16·3 g., 1·2 mol.) were dissoved in acetone (46 ml.), and 10% aqueous sodium hydroxide (16·3 ml.) was added with continuous shaking during 30—60 min. Acetone (4 ml.) was added, and the mixture shaken for 1—2 days and then set aside overnight. After evaporation to small volume the pale yellow lower phase was separated, washed with water, and crystallised from 50% aqueous ethanol (yield, 9 g.). The two anomeric forms were separated

TABLE 1. N-p-*Sulphamylphenylglycosylamines*.

Glycosylamine component	Recryst. from	M. p. (decomp.): present work	M. p. (decomp.): lit.	Rotation: present work *	Rotation: lit.	Found: N (%)	Calc.: N (%)
L-Arabinosylamine	H_2O	191°	194° [a] 195 [b]	+42·7° (0·9, 50% aq. C_5H_5N)	—	9·1	9·2
D-Xylosylamine	50% Aq. EtOH	168—169	150 [b]	−62·3° (0·5)	—	8·9	8·7
D-Galactosylamine (monohydrate)	H_2O–MeOH–EtOH (1 : 20 : 10)	174—175	—	−97° (1·9); −90° (1·8, H_2O)	—	7·8	8·0
D-Galactosylamine	75—80% Aq. EtOH	171—174	142—144 [b]	−110° (1·0)	—	8·3	8·4
D-Mannosylamine (monohydrate)	70% Aq. EtOH	194	202 [a] 196 [b]	−186° (1·0)	−163° (in EtOH); [a] −180° [b]	8·1	8·0
Maltosylamine	80% Aq. EtOH	212—214	236 [b]	−59° (0·9)	+80°, −14° [c]	6·0	5·7
Lactosylamine (trihydrate)	83% Aq. EtOH	210—212	190 [b, d]	−69° (1·7); −76° (1·8, H_2O)	—	5·1	5·1
Cellobiosylamine (tetrahydrate)	83% Aq. EtOH	215—216	—	−81° (0·9); −88° (0·9, H_2O)	—	5·0	4·9 †

[a] Kuhn and Birkofer, *loc. cit.* [b] Schering, Fr.P. 842,726/1939; *Chem. Abs.*, 1940, **34**, 5857. [c] Winthrop Chem. Co. (Klingel and MacLennan), U.S.P. 2,167,719/1939; B.P. 526,747/1940; *Chem. Abs.*, 1941, **35**, 6978. [d] Cavallini and Saccarello, *Chim. et Ind.*, 1942, **24**, 425; *Chem. Abs.*, 1944, **38**, 4257.

* *c* is given in parentheses. The solvent is pyridine unless otherwise stated.

† Formula: $C_{18}H_{28}O_{12}N_2S,4H_2O$.

by repeated fractional crystallisation from 96% ethanol. The crystals first separating were richer in the β-isomer; material richer in the α-isomer was obtained by addition of water to the mother-liquor. Finally, two pure substances were obtained by recrystallisation from ethanol: (i) *N-p*-sulphamylphenyl-β-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate, m. p. 204° (not depressed on admixture with the product of acetylation of *N-p*-sulphamylphenyl-D-glucosylamine), $[\alpha]_D^{22}$ −81° (*c*, 1·0 in C_5H_5N), $[\alpha]_D^{22}$ −56·5° (*c*, 1·7 in $CHCl_3$) (Found: N, 5·5. Calc. for $C_{20}H_{26}O_{13}N_2S$: N, 5·6%); (ii) N-p-*sulphamylphenyl*-α-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*, m. p. 204—205° (decomp.), $[\alpha]_D^{22}$ +203° (*c*, 1·2 in C_5H_5N), $[\alpha]_D^{22}$ +197° (*c*, 0·5 in $CHCl_3$) (Found: C, 48·1; H, 5·2; N, 5·6. $C_{20}H_{26}O_{13}N_2S$ requires C, 47·8; H, 5·2; N, 5·6%). A mixture of the two forms melted at 190—192°.

(*b*) Although varying conditions were employed, condensation of sulphanilamide with D-glucose penta-acetate (Frèrejacque, *loc. cit.*) was unsuccessful.

(*c*) A solution of sulphanilamide (6 g., 3·5 mol.) and D-glucose 2 : 3 : 4 : 6-tetra-acetate (3·4 g., 1 mol.) in 96% ethanol (100 ml.) containing acetic acid (3·4 ml.) was allowed to react at 30° for 1 day. The product was a mixture.

(*d*) A solution of sulphanilamide (1·0 g., 1·2 mol.) and D-glucose 2 : 3 : 4 : 6-tetra-acetate (1·7 g., 1 mol.) in 99% ethanol (50 ml.) containing acetic acid (3·4 ml.) and concentrated hydrochloric acid (3 drops) was refluxed for 1 hour and then kept at room temperature for 3 days. The product (0·5 g.), after recrystallisation from ethanol, had m. p. 204° (decomp.) [not depressed on admixture with the lævorotatory product from (*a*) above], $[\alpha]_D^{21}$ −74° (*c*, 0·9 in C_5H_5N). Later crops resembled the product from (*c*).

N-p-*Sulphamylphenyl*-D-*glucosylamine*.—(*a*) The above product ($[\alpha]_D$ +39·5° in C_5H_5N) (1·5 g.) was suspended in absolute methanol (7 ml.), and 1·0N-sodium methoxide in methanol (0·45 ml.) added. The solution was kept at 30° for 1 hr. and at 0° for 2 days. The product (0·7 g.) was filtered off, and recrystallised from 90% aqueous ethanol as fine needles, m. p. 204°

(decomp.), $[\alpha]_D^{23}$ −117° (*c*, 0·9 in C_5H_5N), $[\alpha]_D^{22}$ −128° (*c*, 0·9 in H_2O). From the rotation it would appear to be the β-form, and no mutarotation was observed.

(*b*) An identical product was obtained in 63% yield by similar treatment of a sample having $[\alpha]_D$ +91° in pyridine. Mixed m. p.s showed the identity of these two products with each other and with the product obtained directly from D-glucose and sulphanilamide.

N-p-*Sulphamylphenyl*-D-*glucosylamine* N : N′ : 2 : 3 : 4 : 6-*Hexa-acetate*.—Acetylation, on the steam-bath with acetic anhydride and anhydrous zinc chloride for 15 min., of *N*-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate (dextro- or lævo-rotatory), or of the unacetylated compound, gave, by addition to water, an identical crystalline solid, N-p-*sulphamylphenyl*-D-*glucosylamine* N : N′ : 2 : 3 : 4 : 6-*hexa-acetate*. Recrystallisation from 25% aqueous ethanol gave needles, m. p. 115°, $[\alpha]_D^{25}$ +77° (*c*, 0·9 in C_5H_5N) (Found : N, 4·85; Ac, 44·2. $C_{24}H_{30}O_{13}N_2S$ requires N, 4·8; Ac, 44·0%).

N-p-*Acetamidobenzenesulphonyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—A solution of D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (0·70 g.) and *N*-acetylsulphanilyl chloride (0·41 g.) in pyridine (5 ml.) was set aside at room temperature for 3 days. After addition of water (60 ml.) the solution was kept for a further 2 days; a crystalline solid was then filtered off (0·8 g.). After recrystallisation from ethanol, N-p-*acetamidobenzenesulphonyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate* had m. p. 197—198° (decomp.), $[\alpha]_D^{23}$ +12·8° (*c*, 1·0 in C_5H_5N) (Found : C, 48·5; H, 5·0; N, 5·23; Ac, 39·9. $C_{22}H_{28}O_{12}N_2S$ requires C, 48·6; H, 5·2; N, 5·2; Ac, 39·6%).

N-p-*Sulphamylphenylcellobiosylamine Hepta-acetate*.—A modification of the Frèrejacque synthesis (Bognár, *loc. cit.*) was employed. A solution of cellobiose hepta-acetate (1·85 g., 1 mol.) and sulphanilamide (0·6 g., 1·2 mol.) in 99% ethanol (30 ml.) containing glacial acetic acid (1 ml.) and concentrated hydrochloric acid (1 drop) was refluxed for 1 hr. The crude product obtained on cooling (1·1 g., 42%) was recrystallised from 90% ethanol, giving N-p-*sulphamylphenylcellobiosylamine hepta-acetate*, m. p. 274—275° (decomp.), $[\alpha]_D^{23}$ −31·4° (*c*, 1·8 in C_5H_5N) (Found : C, 48·6; H, 5·5; N, 3·5. $C_{32}H_{42}O_{19}N_2S$ requires C, 48·6; H, 5·4; N, 3·5%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*galactosylamine*.—A solution of *p*-aminosalicylic acid (3·1 g., 1 mol.), D-galactose (3·7 g., 1 mol.), and ammonium chloride (0·2 g.) in ethanol (80 ml.) was boiled for 45 min. After recrystallisation from ethanol or methanol the *product* (2·6 g., 38%) decomposed at 180° after darkening at 170°, and had $[\alpha]_D$ +134° (*c*, 0·6 in C_5H_5N) (Found : N, 4·2; H_2O, 4·1. $C_{13}H_{17}O_8N,H_2O$ requires N, 4·2; H_2O, 5·4%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—(*a*) Preparation by the Weygand method, as described for sulphanilamide derivatives, gave a crystalline product which, after recrystallisation from aqueous ethanol (18% yield), had m. p. 142° (decomp.), $[\alpha]_D^{23}$ −124° (*c*, 1·0 in C_5H_5N).

(*b*) Under the conditions used for the galactosylamine gave an impure product in 40% yield when boiling was for 30 min. On boiling for 15 min. a relatively pure product was isolated in 71% yield. Recrystallisation from aqueous methanol gave crystals, m. p. 142° (decomp.), $[\alpha]_D^{22}$ −132° (*c*, 0·9 in C_5H_5N) (Found : C, 47·2; H, 5·7; N, 4·2. Calc. for $C_{13}H_{17}O_8N,H_2O$: C, 46·8; H, 5·75; N, 4·2%).

(*c*) Best results were obtained by dissolution of D-glucose (2·0 g., 1·0 mol.) and ammonium chloride (0·1 g.) in warm water (4 ml.), followed by addition of methanol (20 ml.) and *p*-aminosalicylic acid (1·7 g., 1·0 mol.) and shaking at room temperature until all the solid had dissolved. After 24 hours at room temperature crystallisation was induced by scratching. The product (3·15 g., 85%) had m. p. 142° (decomp.), $[\alpha]_D^{23}$ −133° (*c*, 0·8 in C_5H_5N). The rotation of ethanolic or pyridine solutions did not change on storage. An aqueous solution (*c*, 0·9) showed $[\alpha]_D$ −80·5° (5 min.), −72° (20 min.), +5·4° (16 hr.), +23·5° (40 hr., const.). Calculated on the theoretical amount of D-glucose in the solution the $[\alpha]_D$ after 40 hr. is +44°, which is approximately the equilibrium rotation of D-glucose. The yield is double that obtained by Kuhn and Birkofer's original method.

N-(4-*Carbomethoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—(*a*) The above product (1·0 g.), dissolved in methanol (25 ml.), was treated at 0° with excess of ethereal diazomethane. Evaporation to dryness gave a solid which was recrystallised from ethanol (yield, 0·51 g., 50%). After a further recrystallisation from ethanol the *product* had m. p. 187—188° (decomp.), $[\alpha]_D^{22}$ −144° (*c*, 0·5 in C_5H_5N) (Found : N, 4·3. $C_{14}H_{19}O_8N$ requires N, 4·25%).

(*b*) Methyl *p*-aminosalicylate (1·4 g.), D-glucose (1·5 g.), and ammonium chloride (0·15 g.) were treated according to Kuhn's method for 1 hr. The product (1·45 g., 53%), after repeated recrystallisation from ethanol, had m. p. 187—189° (decomp.) [unchanged on admixture with the product from (*a*)], $[\alpha]_D^{22}$ −145° (*c*, 1·0 in C_5H_5N) (Found : N, 4·2; OMe, 8·7. $C_{14}H_{19}O_8N$ requires N, 4·25; OMe, 9·4%).

N-(4-*Carbethoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—Ethyl *p*-aminosalicylate (1·3 g.), D-

glucose (1·3 g.), and ammonium chloride (0·1 g.) were refluxed in 99% ethanol for 2·5 hr. After recrystallisation from 75% aqueous ethanol the *product* (0·7 g.) had m. p. 187° (decomp.), $[\alpha]_D^{22}$ −136° (*c*, 1·0 in C_5H_5N) (Found: N, 4·1; OEt, 12·9. $C_{15}H_{21}O_8N$ requires N, 4·1; OEt, 13·2%).

N-(4-*Carbopropoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—Propyl *p*-aminosalicylate (4·0 g.; m. p. 105°), D-glucose (3·6 g.), and ammonium chlroide (0·3 g.) were refluxed in 99% ethanol for 3 hr. The crude crystalline solid (2·5 g.) was repeatedly recrystallised from aqueous ethanol, giving a *product*, m. p. 135—137° (decomp.), $[\alpha]_D^{22}$ −126° (*c*, 0·9 in C_5H_5N) (Found: N, 4·2. $C_{16}H_{23}O_8N$ requires N, 3·9%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—(*a*) Penta-acetyl glucose was treated with *p*-aminosalicylic acid according to Frèrejacque's method (*loc. cit.*). After 2 weeks at room temperature a solid (20% yield) was obtained. After repeated recrystallisation from ethanol the product had m. p. 183—184° (decomp.), $[\alpha]_D^{22}$ −96° (*c*, 0·5 in C_5H_5N), $[\alpha]_D^{22}$ −69° (*c*, 0·5 in $CHCl_3$) (Found: N, 2·9. $C_{21}H_{25}O_{12}N$ requires N, 2·9%).

(*b*) A solution of D-glucose 2 : 3 : 4 : 6-tetra-acetate (1·7 g., 1 mol.) and *p*-aminosalicylic acid (2·7 g., 3·5 mol.) in 99% ethanol (50 ml.) containing glacial acetic acid (1·7 ml.) was refluxed for 30 min. and set aside for 2 days. The solution was evaporated to one-third volume and a solid (1·2 g.) obtained by addition of water. Further material (1·2 g.) was obtained by concentration of the mother-liquor. After recrystallisation from 50% aqueous ethanol, N-(4-*carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate* had m. p. 185—186° (decomp.) [unchanged on admixture with the product from (*a*)], $[\alpha]_D^{22}$ −99° (*c*, 1·0 in C_5H_5N), $[\alpha]_D^{22}$ −70° (*c*, 1·0 in $CHCl_3$) (Found: C, 52·4; H, 5·2; N, 2·9. $C_{21}H_{25}O_{12}N$ requires C, 52·2; H, 5·2; N, 2·9%).

2 : 3 : 4 : 6-*Tetra-acetyl* 1-(4-*Amino*-2-*hydroxybenzoyl*) D-*Glucose*.—*p*-Aminosalicylic acid (6·0 g., 1 mol.) and acetobromoglucose (20·0 g., 1 mol.) were dissolved in acetone (52 ml.) and treated with 10% sodium hydroxide (20 ml.) as described in the preparation of *N*-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate. The yield was 5·7 g. (30%). After two recrystallisations from ethanol the product was obtained as colourless needles (4·8 g.), m. p. 202° (decomp.), $[\alpha]_D^{21}$ −56° (*c*, 1·7 in $CHCl_3$), $[\alpha]_D^{22}$ −28·5° (*c*, 1·0 in C_5H_5N) [cf. Sannié and Lapin (*loc. cit.*), who record m. p. 191—193° (decomp.), $[\alpha]_D$ −56·9° (in $CHCl_3$)] (Found: C, 51·6; H, 5·3; N, 3·0; Ac, 36·7. Calc. for $C_{21}H_{25}O_{12}N$: C, 52·2; H, 5·2; N, 2·9; Ac, 35·6%). On hydrolysis with sodium methoxide, methyl *p*-aminosalicylate (m. p. 120°) was isolated in 63% yield. Diazotisation and ferric chloride colour tests were positive.

1-(4-*Acetamido*-2-*acetoxybenzoyl*) 2 : 3 : 4 : 6-*Tetra-acetyl* D-*Glucose*.—The above product (1·0 g.) was acetylated by acetic anhydride in pyridine at room temperature for about 7 days. Pyridine was removed under reduced pressure and the residue recrystallised from ethanol (yield, 1·05 g., 89·5%). After a further recrystallisation from ethanol the *product* had m. p. 192—193° (decomp.), $[\alpha]_D^{22}$ −48° (*c*, 1·0 in $CHCl_3$), $[\alpha]_D^{22}$ −40° (*c*, 1·0 in C_5H_5N) (Found: N, 2·5; Ac, 45·1. $C_{25}H_{29}O_{14}N$ requires N, 2·5; Ac, 45·5%). The diazotisation test was negative.

Ultra-violet Absorption Measurements.—All measurements were made on M/20,000-solutions in ethanol. In each of the results below, $\lambda_{max.}$ in Å is followed by the corresponding molecular extinction coefficient (ε): *p*-Aminosalicylic acid: 2370 (7720); 2770 (12,100); 3030 (13,280). Methyl *p*-aminosalicylate: 2420 (7780); 2870 (16,140); 3070 (19,500). Methyl *p*-acetamidosalicylate: 2750 (20,820); 3070 (9000). 4-Acetamido-2-acetoxybenzoic acid: 2670 (20,040). 2 : 3 : 4 : 6-Tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose: 2440 (8260); 3100 (28,320). 1-(4-Acetamido-2-acetoxybenzoyl) 2 : 3 : 4 : 6-tetra-acetyl D-glucose: 2750 (25,180). *N*-(4-Carboxy-3-hydroxyphenyl)-D-glucosylamine: 2280 (10,520); 2680 (15,740); 3000 (12,440). *N*-(4-Carboxy-3-hydroxyphenyl)-D-glucosylamine tetra-acetate: 2300 (9800); 2740 (19,760); 3020 (15,040). *N*-(4-Carbomethoxy-3-hydroxyphenyl)-D-glucosylamine: 2380 (10,440); 2830 (19,580); 3050 (20,640).

We are sincerely grateful to Drs. É. Fodor-Varga, S. Makleit, É. Nemes-Nánási, M. Rákosi, and S. Szabó for carrying out microanalyses and ultra-violet absorption measurements, and to the Hungarian Academy of Science for their support.

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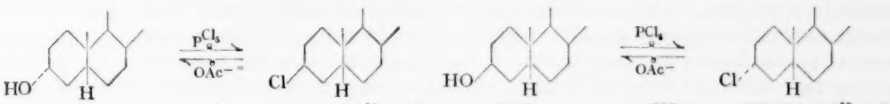
353. *Steroids and Walden Inversion. Part XI.* Acetolysis of the Coprostanyl Halides.*

By R. J. Bridgewater and C. W. Shoppee.

3α- and 3β-Chlorocoprostane have been prepared from coprostanol and *epi*coprostanol, respectively, but only the 3β-bromo-epimeride could be obtained in a state of purity. Acetolysis of the 3α-chloride gave coprost-2-ene and coprostanol, unaccompanied by *epi*coprostanol; conversely, acetolysis of the 3β-chloride or 3β-bromide gave coprost-2-ene and *epi*coprostanol, unaccompanied by coprostanol Absence of racemisation shows that these substitutions take place with inversion of configuration by the bimolecular mechanism S_N2.

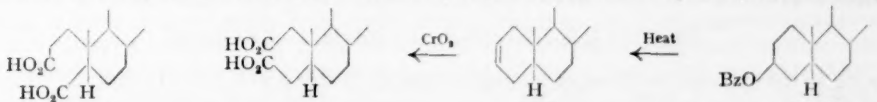
Differences in molecular geometry lead to differences in steric compression which can influence reaction rates and equilibria and so can modify the course of a reaction. Since a previous investigation (Shoppee, *J.*, 1946, 1138) has dealt with the stereochemical course of substitution at $C_{(3)}$ in the cholestane series, it seemed of interest to investigate the parallel problem in the coprostane series.

Treatment of *epi*coprostanol (I) with phosphorus pentachloride in chloroform in the presence of calcium carbonate at 0—25° gave an 80% yield of 3β-chlorocoprostane (II); use of phosphorus pentabromide similarly furnished 3β-bromocoprostane, but thionyl chloride afforded only unsaturated oils.



(I) (II) m. p. 123°, $[\alpha]_D^{15}$ +23° (III) (IV) m. p. 55°/75°, $[\alpha]_D^{19}$ +31°

Similar treatment of coprostanol (III) with phosphorus pentachloride gave 3α-chlorocoprostane (IV) in 40% yield, accompanied by unsaturated hydrocarbon(s). Isolation of the chloride could be achieved only after oxidative destruction of the unsaturated material, whereby an acid, m. p. 202° (dimethyl ester, m. p. 72°), regarded as 2 : 3-*seco*coprostane-2 : 3-dioic acid (VI) because it differed from the known 3 : 4-*seco*coprostane-3 : 4-dioic acid (V), m. p. 245° (dimethyl ester, m. p. 61°), was obtained. This suggests that the accompanying hydrocarbon consisted essentially of coprost-2-ene. Use of thionyl chloride gave as the sole crystalline product coprost-2-ene (VII), which appeared to be identical with a specimen obtained from coprostanyl benzoate (VIII) by pyrolysis and gave a mixture of the 2β : 3α- and 2α : 3β-dibromides, which could not be separated satisfactorily.



(V) (VI) (VII) (VIII)

Coprostanol (III) and phosphorus pentabromide gave a mixture of bromo- and dibromocoprostanes. 3α-Bromocoprostane could not be obtained free from the dibromo-compound; a small amount of the latter was however isolated in a pure state, and is regarded provisionally as 3α : 4β-dibromocoprostane (both Br equatorial) because it exhibited some resistance to debromination whereby a hydrocarbon, m. p. 48°, was produced, which depressed the m. p. (48°) of coprost-2-ene and may be coprost-3-ene. The formation from a monohydric alcohol of a dibromo-compound is probably due to addition of bromine, formed by dissociation of phosphorus pentabromide in chloroform (cf. Shoppee and Summers, *J.*, 1952, 1786), to an intermediate olefin.

The two chlorides (II) and (IV) are stable to hot pyridine; 3β-chlorocoprostane (II) with hot collidine yields coprost-2-ene, whilst this hydrocarbon is obtained from both chlorides by treatment with hot quinoline.

* Part IX, *J.*, 1953, 241; Part X, *J.*, in the press.

The most notable features of the foregoing substitution reactions are the ease of substitution of *epi*coprostanol (I ⟶ II) and the absence here of coprost-2-ene, and the relative difficulty* of substitution of coprostanol (III ⟶ IV) with production of much coprost-2-ene. These observations are consistent with the equatorial character of the 3α-hydroxyl group in *epi*coprostanol as opposed to the polar nature of the 3β-hydroxyl group in coprostanol. Thus lesser steric compression in *epi*coprostanol and greater steric compression in coprostanol affect the formation of the ester–halide complex $RO{\cdot}PCl_4$; whilst the non-planarity of the four centres [3α-oxygen atom, $C_{(3)}$, $C_{(2)}$, and the 2-hydrogen atom (α or β)] in (I) is to be contrasted with the uniplanar arrangement of the four centres [3β-oxygen atom, $C_{(3)}$, $C_{(2)}$, and the 2α(or 4α)-hydrogen atom in (II)], which facilitates the ionic elimination reaction (*E*2) leading to coprost-2-ene. An alternative, and equally probable, path involving the 4α-hydrogen atom leads to coprost-3-ene.

Whereas the epimeric cholestanyl chlorides were found to undergo acetolysis only slowly at 180°, the epimeric coprostanyl chlorides react fairly rapidly with 3M-potassium acetate in acetic acid at 130°. Acetolysis of 3β-chlorocoprostane (II) afforded material which, after alkaline hydrolysis, was resolved into coprost-2-ene and pure *epi*coprostanol (I); absence of coprostanol (III) was proved by exhaustive chromatographic analysis and by use of digitonin. Conversely, acetolysis of 3α-chlorocoprostane (IV) gave a product which, after alkaline hydrolysis, was separated chromatographically into coprost-2-ene and coprostanol (III), unaccompanied by any detectable amount of *epi*coprostanol (I).

The production of only a *single* epimeric acetate in each case shows that a bimolecular acetolysis (S_N2) proceeding with inversion of configuration is solely responsible for the substitution process. Since secondary alkyl halides in non-aqueous media and in the absence of effective basic reagents can afford olefins by the unimolecular elimination mechanism (*E*1), the formation of coprost-2-ene (or coprost-3-ene) in the presence of the weakly basic acetate anion as a result of the expulsion of a proton from an intermediate coprostanyl cation is not unexpected. The slow halogen ionisation stage of mechanism *E*1 would also be the initial stage of a unimolecular acetolysis (S_N1) involving racemisation, but it is clear from the singular formation of the acetates of the epimers (I) and (III) that such unimolecular acetolysis does not occur.

Some kinetic observations have been made on the acetolysis of 3β-bromocoprostane at 94·8° in the presence of sodium acetate. The halide undergoes simultaneous substitution and elimination reactions; the former involves the acetate anion and must be of first order with respect to both halide and acetate, whilst the latter, owing to the ineffectiveness of the acetate anion as a base, should be of first order with respect to the halide and of zero order to acetate. If the initial concentrations of halide and acetate ion are a and b respectively, and the amount x of halide reacting in time t to give stanyl acetate is x_S and to give coprost-2-ene is x_E so that $x = x_S + x_E$, then

$$S\mathrm{d}x/\mathrm{d}t = k[S_N2](a-x)(b-x) \text{ and } E\mathrm{d}x/\mathrm{d}t = k[E1](a-x). \quad . \quad . \quad . \quad (1)$$

Owing to the extreme weakness of hydrogen chloride in dry acetic acid (Davies, Meecham, and Shoppee, to be published shortly), it was necessary to use 3β-bromocoprostane in order to determine residual acetate anion to obtain a measure of the total halide reacting. The concentration of acetate anion was determined by titration with a standard solution of perchloric acid in dry acetic acid, whilst that of coprost-2-ene was estimated colorimetrically by the Liebermann reaction. Owing to the necessity of using the less accessible 3β-bromocoprostane, the number of runs was restricted; it was also unfortunate that the concentration of acetate anion was large (5 : 1) compared with the total amount of halide reacting, so that (1) reduces to :

$$S\mathrm{d}x/\mathrm{d}t = k[S_N\psi1](a-x) \text{ and } E\mathrm{d}x/\mathrm{d}t = k[E1](a-x)$$

whence

$$k[S_N\psi1] + k[E1] = \frac{1}{t}\ln\frac{a}{a-x} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

* The difficulty cannot be purely " spatial " because two bromine atoms can be attached to $C_{(3)}$, *e.g.*, coprostan-3-one with phosphorus pentabromide gives 3 : 3-dibromocoprostane, m. p. 134°, $[\alpha]_D$ +12°.

The average values found from (2) are $k[S_N\psi 1] = 0{\cdot}0023$ hr.$^{-1}$ and $k[E1] = 0{\cdot}0071$ hr.$^{-1}$, and the results show that both the substitution and elimination reactions are of the first order with respect to the bromide.

The situation disclosed in the coprostane series is in striking contrast to that in the cholestane series :

	Chloride (%) involved in elimination reaction $E1$	Chloride (%) involved in substitution reactions	3α-Ol (%) isolated arising by S_N2	3α-Ol (%) isolated arising by S_N1	3β-Ol (%) isolated arising by S_N2	3β-Ol (%) isolated arising by S_N1
3α-Chlorocoprostane	77, 82	22, 17	—	0	100	0
3β-Chlorocoprostane	79, 81	17, 19	100	0	—	0
3α-Chlorocholestane	77	23	—	12	76	12
3β-Chlorocholestane	74	26	70	15	—	15

The results suggest that the stability of the coprostanyl cation is less than that of the cholestanyl cation. Either its life is too short to permit reaction with an external acetate anion and it acquires stability by internal expulsion of a proton, or the rate of reaction with an acetate anion may be so slow relative to the internal depolarisation process that the former is completely excluded. The apparent instability of the coprostan-3-yl cation, compared with the cholestan-3-yl cation, may be a reflexion of the L-shaped character of the coprostane molecule, which leads to repulsions between the polar $C_{(2)}$–H_α and $C_{(4)}$–H_α bonds and the polar $C_{(7)}$–H_α and $C_{(9)}$–H_α bonds comparable in magnitude with these between the $C_{(1)}$–H and $C_{(4)}$–H bonds in the boat conformation of the *cyclo*hexane molecule.

Experimental

For general and experimental directions see *J.*, 1953, 243, 540. Phosphorus pentachloride and pentabromide were sublimed at 40—60°/0·02 mm. For halogenations pure dry chloroform (free from ethanol) was used. Rotations were determined in chloroform.

Coprostan-3α-ol was prepared by hydrogenation of coprostan-3-one (5·5 g.) in methanol–ether (1 : 1) with platinum oxide (cf. Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407). The product, m. p. 100—102°, was purified by chromatography on aluminium oxide; elution with ether–benzene (1 : 24) gave coprostan-3α-ol (3·1 g.), m. p. 116—117° [acetate, m. p. 87—89°, $[\alpha]_D^{18}$ +42° (*c* 1·42)], and further elution with ether–benzene (1 : 24 and 1 : 9) gave coprostan-3β-ol (700 mg.), m. p. 99—101°.

3β-Chlorocoprostane.—Coprostan-3α-ol (1·9 g.; dried at 100°/0·1 mm.), dissolved in chloroform (110 c.c.) containing dry calcium carbonate (3 g.) in suspension, was treated with phosphorus pentachloride (4·5 g., freshly sublimed) added during 1·5 hr. at 0° with shaking. The mixture was shaken for a further 0·5 hr. at 0°, then for 2 hr. at 25°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The crystalline product (2·04 g.) gave no colour with tetranitromethane–chloroform, and recrystallisation from acetone gave *3β-chlorocoprostane* (1·5 g.) as plates, m. p. 122—123°, $[\alpha]_D^{18}$ +22·5° ± 1° (*c* 1·85) [Found (after drying at 90°/0·01 mm. for 2 hr.) : C, 79·7; H, 11·6; Cl, 8·6. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·65; Cl, 8·7%]. The material in the mother-liquor by chromatography on aluminium oxide and elution of the column with pentane gave crystals (230 mg.), which recrystallised from acetone in plates (160 mg.), m. p. 119—121°. The yield was 80%; use of pyridine for calcium carbonate decreased the yield to 40%.

3β-Bromocoprostane.—Coprostan-3α-ol (1·6 g.; dried at 100°/0·1 mm.) in chloroform (65 c.c.) containing a suspension of dry calcium carbonate (5 g.) was treated with phosphorus pentabromide (5·6 g.; freshly sublimed) added during 0·5 hr. at −4° with shaking. The mixture was shaken for a further 0·5 hr. at −4°, 0·25 hr. at 0°, and 3·5 hr. at 20°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The orange crystalline product (1·42 g.) was dissolved in pentane and filtered through a column of aluminium oxide (10 g.); the product, crystallised from acetone, gave *3β-bromocoprostane* (835 mg.) as plates, m. p. 112·5—113·5°, $[\alpha]_D^{20}$ +18° ± 1·5° (*c* 1·24) [Found (after drying at 80°/0·05 mm. for 5 hr.) : C, 71·6; H, 10·3. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·55%]. The mother-liquors yielded a further quantity (136 mg.), m. p. 111·5—113·5°, giving a faint positive reaction in the Liebermann–Burchard test.

Action of Thionyl Chloride.—A solution of coprostan-3α-ol (100 mg.) in ether (5 c.c.) was slowly added to purified thionyl chloride (5 c.c.) in ether (5 c.c) containing dry calcium carbonate (300 mg.) with stirring. After 24 hr. at 20°, the product was isolated in the usual way as an

oil giving a yellow colour with tetranitromethane–chloroform. Chromatography and attempted crystallisation failed to give crystalline material.

Coprostan-3β-ol.—This was prepared by hydrogenation of coprostan-3-one (8·3 g.) in acetic acid containing hydrogen bromide with 10% by wt. of platinum oxide; the reduction product was separated chromatographically into coprostane (14%), coprostan-3α-ol (23%), and coprostan-3β-ol (57%), which crystallised from methanol in needles, m. p. 100—101° [acetate, m. p. 91°, $[\alpha]_D^{18}$ +14·5° ± 1° (*c* 1·37)] (cf. Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1407).

3α-*Chlorocoprostane.*—Coprostan-3β-ol (3 g.; dried at 40°/0·01 mm.), in chloroform (175 c.c.) containing dry calcium carbonate (4·4 g.) in suspension, was treated with phosphorus pentachloride (7·2 g.; freshly sublimed) added during 1·5 hr. at 0° with shaking. The mixture was shaken for a further 1·5 hr. at 0°, then for 19 hr. at 25°, poured into ice-water, and extracted with ether. The extract, after working up in the usual way, gave a neutral oil (3·25 g.), which was chromatographed in pentane on a column of aluminium oxide (90 g.) prepared in pentane. Elution with pentane (300 c.c.) gave a colourless oil (2·2 g.); further elution with benzene (3 × 300 c.c.) gave crystalline fractions (350, 250, and 200 mg.), which by recrystallisation from methanol yielded coprostan-3β-ol (600 mg.), m. p. 101—102°. The foregoing oil was suspended in acetic acid and stirred with a 2% solution of chromium trioxide in 98% acetic acid at 60° for 0·5 hr.; after removal of acetic acid under reduced pressure, the reaction mixture was poured into 2N-sodium carbonate and extracted with chloroform–ether. Evaporation of the dried extract gave material (2·05 g.) which was treated with pentane (200 c.c.); after filtration from an insoluble solid, the pentane solution was passed through a column of aluminium oxide (50 g.) prepared in pentane, and evaporated. The residue (1·2 g.) was crystallised from acetone–methanol (2 : 1), to give 3α-*chlorocoprostane* (730 mg.), m. p. 74—75°, $[\alpha]_D^{19}$ +31° ± 1° (*c* 1·46) [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 79·95; H, 11·65; Cl, 9·0. $C_{27}H_{47}Cl$ requires C, 79·65; H, 11·65; Cl, 8·7%]; a further quantity (210 mg.), m. p. 72—75°, was obtained from the mother-liquor. Elution of the column with benzene (2 × 200 c.c.) and with ether–benzene (1 : 1; 200 c.c.) gave fractions (350, 100, and 50 mg.), which were united and rechromatographed on aluminium oxide (20 g.). Elution of this column with benzene–pentane (1 : 49) gave crystalline material (45 mg.), recrystallised from acetone–methanol to give an unidentified *substance* (20 mg.), m. p. 70—71° [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 84·0; H, 11·9. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%]; elution with benzene–pentane (1 : 1) gave needles (228 mg.), recrystallised from aqueous acetone to give cholest-4-en-3-one, m. p. 79—80°, mixed m. p. 78—80° (characterised as the red 2 : 4-dinitrophenylhydrazone, m. p. 233°), the origin of which is obscure. The solid (260 mg.) insoluble in pentane was recrystallised from aqueous acetic acid, to give 2 : 3-*seco*coprostane-2 : 3-dioic acid, m. p. 201—202°, unchanged by recrystallisation and characterised by treatment with ethereal diazomethane as the *dimethyl* ester, m. p. 72°, after purification by chromatography (elution with benzene–pentane, 1 : 9) and crystallisation from methanol [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 75·1; H, 10·9. $C_{29}H_{50}O_4$ requires C, 75·25; H, 10·9%].

Using similar conditions but reducing the reaction time after addition of phosphorus pentachloride to 0·5 hr. at 0° and 4 hr. at 15° gave a 23% yield of 3α-chlorocoprostane in a polymorphic *form*, needles (from acetone), m. p. 54—55°, solidification and remelting at 74—75° [Found (after drying at 30°/0·01 mm. for 2 hr.): C, 79·45; H, 11·6%]. Replacement of calcium carbonate by dry pyridine gave little or no chloro-compound; grinding coprostan-3β-ol with phosphorus pentachloride in a mortar gave 3α-chlorocoprostane in yields of 5—10%.

Attempted Preparation of 3α-*Bromocoprostane.*—Coprostan-3β-ol (1 g.; dried at 80°/0·05 mm.), in chloroform (60 c.c.) containing dry calcium carbonate (3·3 g.), was treated with phosphorus pentabromide (6·0 g.; freshly sublimed) added during 1 hr. at —8° with shaking. The mixture was then shaken for 0·25 hr. at —5°, 1 hr. at 0°, and 3·5 hr. at 15°, and poured into saturated sodium hydrogen carbonate solution, and the product extracted with ether. The resultant yellow oil was dissolved in pentane (50 c.c.) and filtered through a column of aluminium oxide (15 g.) prepared in pentane. The column was washed with pentane (2 × 50 c.c.), and the filtrate and washings were combined and evaporated to a colourless oil (1·06 g.; positive Beilstein test; weak Liebermann–Burchard test), which was dissolved in acetic acid and stirred with a 2% solution of chromium trioxide in 98% acetic acid at 60° for 0·5 hr. The reaction mixture was poured into water and worked up in the usual way, to give an oil, which was dissolved in pentane (50 c.c.) and filtered through a column of aluminium oxide (15 g.) prepared in pentane. The column was washed with pentane (50 c.c.), and filtrate and washings were united, to give an oil (955 mg.; faint Liebermann–Burchard test); further elution of the column with pentane (50 c.c.) gave a solid (45 mg.), which readily crystallised from acetone to give a

dibromocoprostane in plates, m. p. 97—98°, $[\alpha]_D^{19}$ −5° ± 1° (*c* 1·84) [Found (after drying at 70°/0·04 mm. for 5 hr.): C, 61·5; H, 8·5; Br, 29·85. $C_{27}H_{46}Br_2$ requires C, 61·15; H, 8·75; Br, 30·1%]; the dibromo-compound (20 mg.) was recovered unchanged after treatment with zinc dust (50 mg.) in boiling methanol (5 c.c.) for 0·75 hr., but debromination occurred after 6 hr. to give a hydrocarbon, m. p. 48° after recrystallisation from acetone. This material gave negative Rosenheim and Beilstein tests and depressed the m. p. of coprost-2-ene (48°) to 35°, but there was insufficient material for further identification. The oil (955 mg.) was re-oxidised and worked up as before to give an oil (917 mg.) which was dissolved in pentane (10 c.c.), filtered through a column of neutralised aluminium oxide (5 g.), and followed by pentane (100 c.c.). Evaporation of the combined filtrate and washing gave a colourless oil (900 mg.) which gradually crystallised. Repeated recrystallisation from acetone gave needles, m. p. 104—106°, which appeared to consist of an equimolecular *complex* of 3α-bromocoprostane and the above dibromide [Found (after drying at 20°/0·04 mm. for 18 hr.): C, 65·9; H, 9·45; Br, 23·6. $C_{27}H_{47}Br,C_{27}H_{46}Br_2$ requires C, 66·05; H, 9·55; Br, 24·4%]. The mother-liquors were united and evaporated; the residue was chromatographed on a long column (8·5 cm.) of aluminium oxide (10 g.) and eluted with pentane (6 × 5 c.c.), to give fractions weighing 0, 10, 156, 130, 10, and 2 mg. respectively. Fractions 3 and 4 crystallised when rubbed with acetone, and were united, and recrystallised from acetone, to give impure 3α-bromocoprostane (177 mg.), m. p. 80—84°, $[\alpha]_D^{19}$ +27·5° ± 1° (*c* 1·45) [Found (after drying at 70°/0·01 mm. for 3 hr.): C, 68·5; H, 9·9; Br, 21·5. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·5; Br, 17·7%].

Action of Thionyl Chloride.—A solution of coprostan-3β-ol (100 mg.) in ether (5 c.c.) was slowly added to purified thionyl chloride (5 c.c.) in ether (5 c.c.) containing a suspension of calcium carbonate (300 mg.). After 24 hr. at 20°, the reaction product was isolated in the usual way as an oil which was chromatographed on a column of aluminium oxide (8 g.) prepared in pentane. Elution with pentane (4 × 5 c.c.) gave fractions: 1, nil; 2, needles (10 mg.), m. p. 46—47° after crystallisation from acetone; 3, needles (20 mg.), m. p. 47—48° after crystallisation from acetone; 4, crystals (3 mg.); the material in fractions 2 and 3 consisted of coprost-2-ene, mixed m. p. 48°. Various modifications of temperature, medium ($CHCl_3$), and reaction time yielded oils from which in some cases coprost-2-ene could be isolated.

Coprost-2-ene. (*a*) 3α-Chlorocoprostane was refluxed for 6 hr. with quinoline; after removal of the base under reduced pressure, the product was dissolved in ether, washed successively with 2N-hydrochloric acid, water, 2N-sodium carbonate, and water, dried, and evaporated, to give *coprost-2-ene*, m. p. 47—48°, $[\alpha]_D^{22}$ +23° ± 1° (*c* 1·59) [Found (after drying at 35°/0·01 mm. for 4 hr.): C, 87·15; H, 12·9. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%].

(*b*) 3β-Chlorocoprostane by similar treatment with quinoline gave coprost-2-ene, m. p. 48°; a mixed m. p. with the specimen obtained as under (*a*) showed no depression.

(*c*) Coprostan-3α-yl benzoate (4·5 g.; m. p. 85—86°) was pyrolysed at 320°/10 mm. in an atmosphere of carbon dioxide and the product distilled at 0·01 mm.; the distillate was dissolved in ether and the solution washed with 2N-sodium carbonate, then with water, dried, and evaporated. Chromatography on a column of aluminium oxide (50 g.) prepared in pentane gave by elution with pentane coprost-2-ene (1·2 g.), m. p. 47—48°, after crystallisation from acetone. Further elution of the column with benzene–pentane mixtures gave oils (800 mg.), followed by unchanged coprostanyl-3α-yl benzoate (2 g.).

(*d*) Coprostan-3β-yl benzoate (1·6 g.; m. p. 124—125°) was pyrolysed similarly; chromatography of the reaction product gave by elution with pentane coprost-2-ene (520 mg.) in needles, m. p. 46—48°, $[\alpha]_D^{22}$ +24·5° ± 1° (*c* 1·52), after crystallisation from acetone.

Coprost-2-ene, by treatment in ether with an ethereal solution of 1 mol. of bromine at 20°, gave an oil which crystallised after some days; recrystallisation from acetone gave a product, m. p. 76—96°, regarded as a mixture of 2α : 3β- and 2β : 3α-dibromocoprostane [Found (after drying at 40°/0·01 mm. for 5 hr.): C, 61·3; H, 8·9. Calc. for $C_{27}H_{46}Br_2$: C, 61·15; H, 8·75%], which could not be separated by further crystallisation of the material available.

Action of Pyridine and s-*Collidine.*—3α-Chlorocoprostane was recovered unchanged as needles, m. p. 75—76°, mixed m. p. 74—76°, after 3 hr.' refluxing with pyridine or 6 hr.' with *s*-collidine. 3β-Chlorocoprostane was likewise recovered unaltered, m. p. 124°, mixed m. p. 123—124°, after similar treatment.

Acetolysis of 3α-*Chlorocoprostane.*—3α-Chlorocoprostane (250 mg.), freshly fused potassium acetate (2·5 g.), and anhydrous acetic acid (7 c.c.) were refluxed with exclusion of moisture for 6 hr. The cooled mixture was poured into water and extracted with ether, and the product hydrolysed by refluxing 4% methanolic potassium hydroxide for 3 hr. After addition of a little water and saturation with carbon dioxide, methanol was removed under reduced pressure

and the product extracted with ether. The resulting oil (238 mg.) was chromatographed on aluminium oxide (27 g.), prepared in pentane, 25-c.c. eluates being used. Elution with pentane [Fr. A 1—3] gave coprost-2-ene (175 mg.), m. p. 46°, after crystallisation from ether–methanol; benzene–pentane mixtures [Fr. A 10—12] and ether–benzene (1 : 24) [Fr. A 13] gave no significant amounts of material. Elution with ether–benzene (1 : 4) gave fractions A 14 (50 mg.; m. p. 101—102°) and A 15 (5 mg.; m. p. 101°), after crystallisation from methanol, consisting of pure coprostan-3β-ol, whilst use of ether–benzene (1 : 1) and ether yielded no material. The m. p. of fractions A 14 and A 15 were unaltered by recrystallisation from methanol [A 14 : mixed m. p. with coprostan-3β-ol, 100—101°; mixed m. p. with coprostan-3α-ol, 74—80°]; the total weight of material eluted from the column was 232 mg. A portion (28 mg.) of fraction A 14 was rechromatographed and by elution with ether–benzene (1 : 19) gave fractions: B 7 (1 mg.; m. p. 100—101°), B 8 (8 mg.; m. p. 100—101°), B 9 (8 mg.; m. p. 99—101°), B 10 (8 mg.; m. p. 100—101°), B 11 (0·2 mg.), all undepressed by admixture with coprostan-3β-ol and characterised by conversion into the acetate, m. p. 90°, mixed m. p. 90—91°.

In a second similar experiment 3α-chlorocoprostane (250 mg.) gave a hydrolysed product (236 mg.) resolved by chromatography on a slightly less active aluminium oxide into coprost-2-ene (187 mg.) eluted with pentane, oil (1 mg.) eluted with benzene–pentane, oil (1·5 mg.) eluted with benzene, and coprostan-3β-ol [Fr. C 12 (1 mg.; m. p. 100°); C 13 (18·5 mg.; m. p. 99—101°, mixed m. p. 100—101°), C 14 (18 mg.; m. p. 100—101°, mixed m. p. 100—101°), and C 15 (4 mg.; m. p. 100°)] eluted with ether–benzene (1 : 24) and characterised by conversion into coprostan-3β-yl acetate, m. p. 89—90°, mixed m. p. 89—91°. The total weight of material eluted from the column was 231 mg.

Acetolysis of 3β-*Chlorocoprostane.*—3β-Chlorocoprostane (250 mg.) was subjected to acetolysis under the same conditions as were used for the 3α-epimeride, and furnished a hydrolysed product (230 mg.), which was chromatographed on aluminium oxide (27 g.) prepared in pentane, 25-c.c. eluates being used. Elution with pentane (Fr. D 1—4] gave coprost-2-ene (179 mg.), m. p. 46°, after crystallisation from ether–methanol. Benzene–pentane (1 : 4 and 1 : 1) [Fr. D 5—9] gave oils (3·5 mg.); benzene [Fr. D 10—13] also gave oil (1·5 mg.). Elution with ether–benzene (1 : 1) gave Fr. D 14 (4 mg.; m. p. 110° after crystallisation from methanol), whilst use of ether gave Fr. D 15 and D 16 (which crystallised spontaneously and were united: 37 mg., m. p. 111°). The m. p. of fractions D 14 and D 15 + 16 were unchanged by recrystallisation from methanol (D 15 + 16: mixed m. p. with coprostan-3α-ol, 110—111°; mixed m. p. with coprostan-3β-ol, 81—84°), and neither gave a precipitate with digitonin in 90% methanol. The total weight of material eluted from the column was 225 mg.

In a repetition, 3β-chlorocoprostane (250 mg.) gave a hydrolysed product (235 mg.), resolved by chromatography on a slightly less active aluminium oxide into coprost-2-ene (185 mg.) eluted with pentane, oil (1 mg.) eluted with benzene–pentane (1 : 4 and 1 : 1), oil (0·5 mg.) eluted with benzene, and coprostan-3α-ol [Fr. E 11, nil; E 12 (4·5 mg.; m. p. 110—111°, mixed m. p. 110°); E 13 (24 mg.; m. p. 110°, mixed m. p. 110°); E 14 (14 mg.; m. p. 110—111° mixed m. p. 110—111°); E 15 (2 mg.; m. p. 110°, mixed m. p. 110—111°); E 16 (0·5 mg.)], eluted with ether–benzene (1 : 24), and characterised by conversion (Fr. E 13 and 14] into coprostan-3α-yl acetate, m. p. 87—88°, mixed m. p. 88°. The total weight of material eluted from the column was 231 mg.

Use of potassium acetate (250 mg.) in anhydrous propionic acid (b. p. 141°; 7 c.c.) for 4 hr. furnished coprost-2-ene and coprostan-3α-ol in essentially the same proportion (4 : 1). Use of potassium acetate in anhydrous formic acid (b. p. 100·5°) slowed down the reaction, and only 20% of 3β-chlorocoprostane was decomposed in 6 hr. as judged by estimation of chloride ion as silver chloride in the acetolysis product. Use of potassium acetate (400 mg.) in acetic acid–dioxan [3·2 c.c. (1 : 3·5), b. p. ~107°] for 24 hr. and chromatography led to recovery of 92% of the 3β-chlorocoprostane in the first three pentane eluates.

*Chromatographic Separation of Coprostan-*3α-*ol and* -3β-*ol.*—The epimerides (25 mg. each) were dissolved in pentane and chromatographed on aluminium oxide (3 g.) prepared in pentane, with 5-c.c. eluates No material was eluted with benzene or ether–benzene (1 : 49); use of ether–benzene (1 : 24) gave fractions: 1, 2 mg.; 2, 12 mg., m. p. and mixed m. p. with coprostan-3α-ol, 111°; 3, 9·5 mg., m. p. 111°, mixed m. p. with coprostan-3α-ol, 110—111°; 4, 6 mg., m. p. 90—100°, consisting of a mixture of the epimerides; 5, 15·5 mg., m. p. 101—102°, mixed m. p. with coprostan-3β-ol, 100—101°; 6, 1·5 mg., m. p. 100°; 7, 0·5 mg.; total 47 mg.

Acetolysis of 3β-*Bromocoprostane.*—Accurately weighed amounts of 3β-bromocoprostane (90·0 + 0·1 mg.) with a standard solution (6·0 c.c.) of sodium acetate in anhydrous acetic acid (made by dissolution of sodium carbonate in acetic acid and standardisation against a 0·49N-

solution of perchloric acid in acetic acid with tropæolin as indicator) were introduced into a series of sealed ampoules and kept in a thermostat at 94·8°. At various times an ampoule was removed and cooled, and the contents were transferred into a graduated flask (10 c.c.) with chloroform. Aliquots of the chloroform solution were used as follows: (1) 2·0 c.c. were titrated against 0·49N-perchloric acid in anhydrous acetic acid (tropæolin), to determine the amount of acetate, whilst a similar titration on an aliquot of a similar run without 3β-bromocoprostane was made, the difference giving the amount of acetate used in the reaction, which is equivalent to the quantity of bromide decomposed; (2) 1·0 c.c. was pipetted on to anhydrous sodium carbonate (1·2 g.) in a glass mortar, and the mass freed from chloroform in a vacuum-desiccator, ground to a fine powder, and extracted (Soxhlet) with chloroform for 12 hr.; the extract was made up to 10 c.c. and the amount of coprost-2-ene in samples of this solution determined by use of the Liebermann–Burchard test. This was done by diluting the sample with chloroform to 10 c.c. and treating this with 9 : 1 acetic anhydride–concentrated sulphuric acid (2·0 c.c.); after 45 min. the intensity of colour was measured in a standard cell on a Spekker photometer and the amount of coprost-2-ene present read off from a calibration curve, previously prepared by using standard solutions of coprost-2-ene, with an error of ~3%. The results are tabulated.

Concn. of 3β-bromocoprostane, 0·0332 mole/l. Concn. of NaOAc, 0·1829 mole/l.

t (hr.)	10^4x	10^4x_S	10^4x_E	$k[S_N\psi 1] + k[E1]$ (hr.$^{-1}$)	$k[S_N\psi 1]$ (hr.$^{-1}$)	$k[E1]$ (hr.$^{-1}$)
26	0·575	0·126	0·389	0·0116	0·0028	0·0088
44	0·638	0·159	0·479	0·0092	0·0022	0·0070
90	1·00	0·255	0·746	0·0080	0·0020	0·0060
139	1·32	0·343	0·981	0·0081	0·0021	0·0060
190	1·67	0·379	1·290	0·0101	0·0023	0·0078
243	1·96	0·430	1·530	—	—	—

3 : 3-*Dibromocoprostane*.—Coprostan-3-one (100 mg.), in chloroform (15 c.c.), was treated with phosphorus pentabromide (600 mg.; freshly sublimed) during 20 min. at 0°. After 1 hr. at 0° and 12 hr. at 18°, working up in the usual way gave a solid which by recrystallisation from methanol gave needles of 3 : 3-*dibromocoprostane*, m. p. 134°, $[\alpha]_D^{18}$ +12° ± 1° (*c* 1·785) [Found (after drying at 90°/0·05 mm. for 2 hr.): C, 61·1; H, 8·7. $C_{27}H_{46}Br_2$ requires C, 61·15; H, 8·75%].

One of us (R. J. B.) thanks the Chemical Society, and the other (C. W. S.) thanks the Royal Society, for grants which have partly defrayed the cost of this work.

UNIVERSITY COLLEGE, SWANSEA, UNIVERSITY OF WALES. [*Received, January 20th*, 1953.]

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354. *Stereospecificity in Thermal Elimination Reactions. Part III.* The Pyrolysis of (−)-Menthyl Benzoate.*

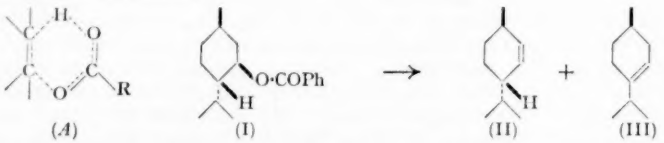
By D. H. R. BARTON, A. J. HEAD, and R. J. WILLIAMS.

The pyrolysis of (−)-menthyl benzoate to give a mixture of (+)-*p*-menth-2- and -3-ene and benzoic acid has been investigated by both static and dynamic methods. The reaction is homogeneous and unimolecular in mechanism. The rate-constant equation can be represented by the expression $k = 10^{11}e^{-38,100/RT}$ sec.$^{-1}$. The ratio of Δ^2- to Δ^3-olefin produced in the decomposition is approximately 1 : 2. The formation of the latter hydrocarbon by the unimolecular mechanism confirms the correlation previously proposed (Barton, *J.*, 1949, 2174) between the mechanism of ester pyrolysis and its stereospecificity.

THE thermal decomposition of esters to give olefins and carboxylic acids is a smooth reaction which is frequently of preparative value. It has been suggested (Hurd and Blunck, *J. Amer. Chem. Soc.*, 1938, **60**, 2419) that such reactions are unimolecular, proceeding through a transition state of type (*A*). Granted this, then *cis*-stereospecificity for the reaction follows (Barton, *J.*, 1949, 2174; Barton and Rosenfelder, *J.*, 1949, 2459;

* Part II, *J.*, 1952, 453.

Alexander and Mudrak, *J. Amer. Chem. Soc.*, 1950, **72**, 1810, 3194; 1951, **73**, 59; Arnold, Smith, and Dodson, *J. Org. Chem.*, 1950, **15**, 1256). It must be emphasized, however, that this conclusion is only justified theoretically if the mechanism can be *proved* to be both homogeneous and unimolecular.



(*A*) (I) (II) (III)

The present investigation is concerned with the pyrolysis of a typical ester, (−)-menthyl benzoate (I), to give a mixture of (+)-*p*-menth-2- (II) and -3-ene (III) and benzoic acid. The formation of the latter hydrocarbon, together with the appropriate mechanistic study, provides the first demonstration of *cis*-elimination in a carboxylic ester pyrolysis of authenticated homogeneous and unimolecular character. A corresponding investigation on

FIG. 1.

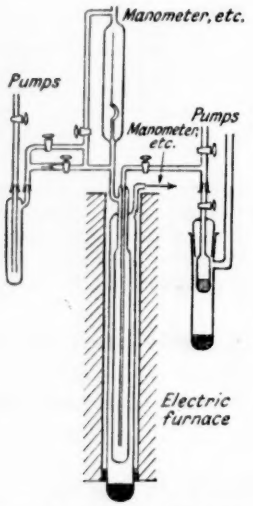
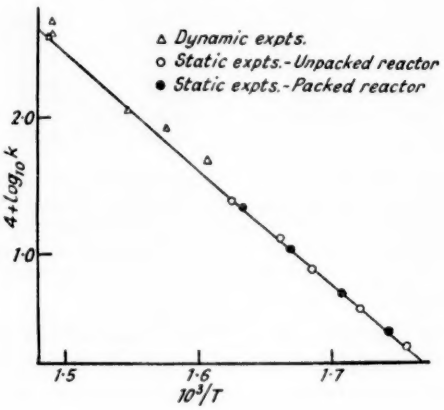


FIG. 2.



xanthate decomposition has been reported recently by O'Connor and Nace (*J. Amer. Chem. Soc.*, 1952, **74**, 5454).

In previous studies of the thermal decomposition of the related (−)-menthyl acetate (McNiven and Read, *J.*, 1952, 2067; Wibaut, Beyerman, and van Leeuwen, *Rec. Trav. chim.*, 1952, **71**, 1027, and references there cited) *cis*-elimination was adequately established by product analysis, but no kinetic or other criterion of reaction mechanism was applied.

EXPERIMENTAL

Materials.—(−)-Menthyl benzoate was prepared by benzoylation of (−)-menthol in pyridine at room temperature. Recrystallisation from methanol gave the pure benzoate, m. p. 56°, $[\alpha]_D$ −86·9° (*c*, 8·8 in $CHCl_3$).

Apparatus.—(i) *Static experiments.* The apparatus and technique were as described in Part II (*loc. cit.*). In order to overcome difficulties caused by the low vapour pressure of (−)-menthyl benzoate, the ordinary storage trap was replaced by a large cylindrical bulb fitted with a thermometer pocket and heated by external electrical windings. The benzoate was outgassed *in vacuo* at 140°. A reservoir temperature of 200° was sufficient to introduce 20 mm. of (−)-menthyl benzoate vapour.

(ii) *Dynamic experiments.* The apparatus used was essentially as described in Part II (*loc. cit.*) except that the reactor was modified to the improved type illustrated in Fig. 1. This

had the advantage of enlarging greatly the volume of the reactor at constant temperature. The technique for carrying out the experiments was as before except that (i) no capillary leak was needed for controlling the input of (−)-menthyl benzoate vapour, (ii) *p*-dichlorobenzene was used as reflux liquid for heating the storage trap, and (iii) the total products of reaction were collected in one trap only (at −80°).

The products were analysed as follows. The products were washed out of the trap quantitatively with chloroform and the solution made up to 25 ml. A 10-ml. portion of this solution was cautiously evaporated, carbon dioxide-free distilled water added, and the dissolved benzoic acid titrated in the usual way. A number of control experiments showed that no benzoic acid was lost in this procedure and that the accuracy of the determinations was ±2%. The residual chloroform solution was then analysed for (+)-*p*-menth-2- and -3-ene as in Part II (*loc. cit.*).

The following experiments were carried out to test the adequacy of the analytical technique. (i) The benzoate (300 mg.) was heated in a sealed and evacuated tube at 200° for 1 hour. No detectable amount of benzoic acid was produced. (ii) The menthene mixture (160 mg.), obtained as a by-product (see Part II, *loc. cit.*) in the preparation of (−)-menthyl chloride, in chloroform (2 ml.), was treated with an equal weight of benzoic acid overnight at room temperature. No reduction in specific rotation was observed. (iii) (−)-Menthyl benzoate (59·1 mg.) in chloroform (10 ml.) was treated with hydrogen chloride as for the analysis of the menthene mixture (see Part II, *loc. cit.*). There was no detectable change in rotation.

Results

Static Experiments.—The kinetics of the decomposition were studied in both empty and packed reactors, the latter having an approximately six-fold increase in surface area : volume ratio. Contrary to experience in the pyrolysis of (−)-menthyl chloride (Part II, *loc. cit.*) reproducible results were soon attained (after about 10 runs) and it is clear that the ester decompositions are far less prone to exhibit heterogeneity than are those of chlorinated hydrocarbons. The reaction showed first-order kinetics to better than 50% decomposition, with no indication of induction periods. Within the limited pressure range accessible, the first-order rate constant was independent of initial pressure (see Table 1; these results refer to the packed

Table 1.

At 587·1° K		At 598·6° K		At 587·1° K		At 598·6° K	
p_0, mm.	10^3k, sec.$^{-1}$	p_0, mm.	10^3k, sec.$^{-1}$	p_0, mm.	10^3k, sec.$^{-1}$	p_0, mm.	10^3k, sec.$^{-1}$
2·7	0·63	3·0	1·17	21·2	0·54	21·4	1·09
10·9	0·58	11·0	1·10			27·1	1·10
15·1	0·54	14·8	1·06				

reactor). The rate-constant results over the temperature range 568·9° to 614·6° K are summarised in Table 2. The best straight line drawn through the points on the corresponding Arrhenius

Table 2.

Temp., K	No. of runs	Mean 10^3k, sec.$^{-1}$	Mean error (%) of the mean k *	Temp., K	No. of runs	Mean 10^3k, sec.$^{-1}$	Mean error (%) of the mean k *
Unpacked reactor.				*Packed reactor.*			
568·9°	3	0·209	1·3	573·5°	5	0·274	0·6
580·6	6	0·392	1·3	585·1	9	0·524	1·3
593·1	9	0·774	0·8	598·6	7	1·10	0·9
601·5	6	1·30	0·7	611·6	7	2·22	0·4
614·6	6	2·49	1·2				

* Given by $100 \times \sqrt{\Sigma(x-\bar{x})^2/n(n-1)}/\bar{x}$, where the symbols have the usual significance.

plot (Fig. 2) by visual inspection indicated an approximate rate constant equation of $k = 10^{11}e^{-38,100/RT}$ sec.$^{-1}$. Because of the experimental difficulties associated with pyrolytic work on compounds of very low vapour pressure, we do not attach error limits to this equation. The homogeneity of the reaction is clearly demonstrated. The addition of propylene or of nitric oxide, even in major amounts, had no significant effect (see Table 3; the figures refer to the packed reactor) on the rate of decomposition; in every run the kinetics remained of the first order.

Dynamic Experiments.—(i) *Stoicheiometry.* A necessary condition for establishing the simple stoicheiometry mentioned above is that the products of decomposition (the menthenes and the benzoic acid) should be stable under the reaction conditions chosen. The stability

of the mixed menthenes follows from the work recorded in Part II (*loc. cit.*). The stability of benzoic acid was shown (*a*) by introducing 20 mm. of the acid into the reactor for static experiments at 615° K and noting that there was no change in pressure during a period corresponding to several half-lives of the ester, and (*b*) by passing benzoic acid vapour (at 13·9 mm.; contact time 116 sec.) through the reactor for dynamic experiments at 671° K and noting 99% recovery of acid by weight (confirmed by direct titration). The stability of benzoic acid under the conditions chosen also follows from Moser's work (*Helv. Chim. Acta*, 1931, **14**, 971).

TABLE 3.

p_0, mm., of ester	p, mm., of addend	$100p/p_0$	10^3k, sec.$^{-1}$	p_0, mm. of ester	p, mm., of addend	$100p/p_0$	10^3k, sec.$^{-1}$
Propylene at 586·1° K.				*Nitric oxide at* 594·7° K.			
—	—	—	0·54 *	—	—	—	0·85 *
20·6	0·22	1·1	0·54	20·2	0·92	4·6	0·83
20·8	1·68	8·1	0·54	20·5	7·72	38	0·84
19·7	2·4	12	0·50	20·5	19·6	95	0·82
22·0	8·7	40	0·51	21·0	20·4	96	0·82
22·1	18·2	82	0·53				
21·3	29·6	139	0·51				

* Mean of control determinations carried out just before the inhibitor experiments.

TABLE 4.*

Temp., K	p, mm.	Contact, time, sec.	Decomp., %	10^3k, sec.$^{-1}$ Found	10^3k, sec.$^{-1}$ Calc.	Loss, %	(+)-*p*-Menth-2-ene, %	$[\alpha]_D$ of (+)-*p*-menth-3-ene, calc
672°	12·3	74	94·2	3·9	3·6	−1·0	—	—
671	15·0	70	94·4	4·1		0·0	—	—
671	15·0	70	79·3	2·3	3·5	+1·0	—	—
671	15·2	63	96·0	5·1		0·0	—	—
646	4·3	178	86·5	1·13	1·15	+1·2	—	—
634	4·6	169	75·6	0·84	0·66	−1·3	—	—
622	4·7	178	57·5	0·48	0·37	−0·9	—	—
647	—	—	96·2	—	—	—	35	+117°
647	—	—	96·2	—	—	—	33	+117
644	—	—	90·9	—	—	—	32	+117
628	—	—	82·5	—	—	—	36	+117

* The last four runs (for menthene ratio) involved the passage of approx. 650 mg. of ester.

Convincing evidence for simple stoicheiometry was obtained in dynamic experiments in the following way. The reaction products were dissolved in ethanol and made up to 25 ml. A 10-ml. portion of the solution was largely diluted with boiled-out distilled water and titrated for benzoic acid in the usual way. To a further 10-ml. portion there was added a known volume of N/20-aqueous potassium hydroxide approx. equivalent to 2·5 times the amount of benzoate pyrolysed, and the solution was refluxed overnight (soda-lime guard tube). The solution was then largely diluted with boiled-out distilled water and the excess of potassium hydroxide titrated in the usual way. The appropriate blank experiments were run at the same time. In this way the amounts of benzoic acid and of unchanged (−)-menthyl benzoate were determined. In two experiments at 631° and 643° K (11·4 and 17·6 mm. pressure respectively), involving the passage of 319 and 488 mg. of ester, balances of 100 and 102% respectively were obtained.

(ii) *Kinetics.* After the first few dynamic runs, the rate of decomposition became reproducible. The rate constants were calculated, first-order kinetics being assumed, by the equation already given (*J.*, 1949, 148). The results are summarised in Table 4 (see also Fig. 2). It will be seen that the rates observed were somewhat higher than those deduced from the rate-constant equation for static runs (see above). The latter are, of course, more reliable.

(iii) *Menthene ratio.* The percentage of (+)-*p*-menth-2- and hence of -3-ene is indicated in Table 4 for suitable runs. The calculated specific rotation for (+)-*p*-menth-3-ene is somewhat higher than that ($[\alpha]_D$ +109°) accepted in Part II (*loc. cit.*).

DISCUSSION

The thermal decomposition of (−)-menthyl benzoate follows first-order kinetics, the rate constants being invariant with pressure. The reaction is homogeneous, exhibits no induction periods even at the lowest temperatures at which rates were measured, and is totally unaffected by addition of propylene or nitric oxide even in major amounts. These facts are adequate to exclude radical or radical-chain mechanisms and to establish beyond doubt that the decomposition is a true homogeneous unimolecular reaction.

The analysis of the menthene ratio (see Results section) shows that approximately twice as much Δ^3- as Δ^2-menthene is formed. The ratio is rather less than that found for pyrolysis of (−)-menthyl chloride (Part II, *loc. cit.*). The formation of the (+)-*p*-menth-3-ene provides a further unambiguous demonstration of the correctness of our general thesis as to the relationship between *cis*-elimination and unimolecularity of mechanism in thermal elimination reactions—in this case for a typical ester decomposition. In particular the results justify our previous assumptions (Barton, *loc. cit.*; Barton and Rosenfelder, *loc. cit.*) with regard to benzoate pyrolyses.

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, February 11th*, 1953.]

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355. *The Dissociation Constants of Thiosulphuric Acid.*

By F. M. PAGE.

The second dissociation constant of thiosulphuric acid has been measured at several ionic strengths by means of a glass electrode. The value extrapolated to zero ionic strength is 0·019. The first dissociation constant has been estimated.

THE rate of the reaction between ferric salts and sodium thiosulphate is affected by the hydrogen-ion concentration (Holluta and Martini, *Z. anorg. Chem.*, 1925, **144**, 321). One factor contributing to this effect is the incomplete dissociation of thiosulphuric acid. It was expected that a significant amount of the total thiosulphate in a reaction mixture would be present as $HS_2O_3^-$, and, if the solution were sufficiently acid, as undissociated thiosulphuric acid $H_2S_2O_3$. The concentration of free thiosulphate ion in the reaction mixture can be calculated if the two dissociation constants of thiosulphuric acid are known. The first dissociation constant has never been measured, although its magnitude has been estimated by analogy with sulphuric acid (Jellinek, *Z. physikal. Chem.*, 1911, **76**, 257). Since values reported for the second dissociation constant are widely scattered, it was decided to make a fresh determination of the dissociation constants of thiosulphuric acid under the same experimental conditions as in the kinetic investigation of the ferric–thiosulphate reaction (Page, in the press).

The dissociation constant of a monobasic acid can be determined by measuring the concentrations of dissociated and undissociated forms of the acid in equilibrium in a solution of known hydrogen-ion concentration. This is conveniently done by adding a known amount of a strong acid, which can be considered as completely dissociated, to a known amount of a salt of the acid under investigation, and determining the hydrogen-ion concentration in the resulting mixture with a glass electrode. If the acid is polybasic, this method leads to an "apparent dissociation constant" which is a function of the hydrogen-ion concentration. The various dissociation constants of the polybasic acid can be measured by determining this apparent dissociation constant over a wide range of hydrogen-ion concentration.

Decomposition of Thiosulphuric Acid.—Acid solutions of sodium thiosulphate rapidly decompose, forming the sulphite ion and free sulphur; $HS_2O_3^- \longrightarrow S + HSO_3^-$. The sulphur is visible as a faint opalescence when its amount exceeds the limit set by its solubility (10^{-4} g.-atom/l.). If the initial concentration of thiosulphate ion exceeds 10^{-2}M, the proportion lost by undetected decomposition will be less than 1%, but it may be substantial in more dilute solutions.

The sulphurous acid produced during the decomposition will also affect the hydrogen-ion concentration. If a small amount of the completely dissociated acid is added to the thiosulphate solution, most of the added hydrogen ions will go to form bisulphite ions,

since the dissociation constant of this ion (10^{-5}) is very much smaller than that of the ion $HS_2O_3^-$. It was found that in solutions of pH 4·5—6·0, thiosulphuric acid appeared to have a dissociation constant of the order of 10^{-5}. This value rose rapidly with increasing acidity, reaching 5×10^{-2} at pH 3·5. The effect of traces of sulphurous acid will be less important in more acid solutions, because all the sulphurous acid will be in the undissociated form, and hydrogen ion thus lost will be a negligible fraction of the total acid added.

Calibration of the Glass Electrode.—The glass electrode measures the activity of the hydrogen ions in a solution. The algebraic equations derived below involve the concentration of hydrogen ions, and it is necessary to convert the measured activities into concentrations before calculating the dissociation constants. This can be done by using estimated activity coefficients, but the necessity for the conversion can be avoided by a suitable calibration of the glass electrode.

The measurement of hydrogen-ion activity by the glass electrode is essentially a series of measurements of the potential of the cell

Glass electrode | Solution X (A) || Satd. KCl (B) | Calomel electrode

There are two unknown junction potentials in this cell—at A and B. The usual calibration of the glass electrode with a standard buffer solution allows for the asymmetry potential of the glass electrode at junction A, but may overcompensate for the liquid-junction potential at B. If the glass electrode is calibrated with a solution whose ionic strength is the same as that of the solution under examination, then the liquid-junction potential at B, and any salt effect on the asymmetry potential at A, will be the same during the experiment as during the calibration, and the difference between the observed potentials will be given by

$$E_{\text{exp.}} - E_{\text{calib.}} = (\boldsymbol{R}T/\boldsymbol{F}) \log_e a_{\text{H}^+,\,\text{exp.}}/a_{\text{H}^+,\,\text{calib.}}$$

where a_{H^+} is the activity of the hydrogen ion, and $E_{\text{exp.}}$ and $E_{\text{calib.}}$ refer respectively to the experimental and the calibrating cell. In this equation, each activity can be replaced by the product of the appropriate concentration and activity coefficient. The two solutions used during the calibration and the experiment have similar compositions and the activity coefficients of the ions will be the same. The difference in the potentials of the experimental and the calibrating cell is therefore a measure, not only of the ratios of the activities of the hydrogen ions in the two cells, but also of the ratios of the concentrations.

It is important that the calibrating solution should differ from the experimental solution as little as possible. In the present work the electrode was calibrated with solutions containing perchloric acid and sodium perchlorate, and in the experimental solutions a portion of the sodium perchlorate was replaced by sodium thiosulphate, the total ionic strength being kept constant.

Experimental.—All materials used were of the best available grade of analytical reagent. The sodium thiosulphate solution was standardised against potassium iodate, and the perchloric acid by reference to potassium hydrogen phthalate. The pH of the sodium perchlorate solution lay within the range 6·8—7·2, showing that no important quantities of free acid or alkali were present. All water had been distilled from a Pyrex-glass still, and was freshly boiled to expel dissolved gases. All solutions were brought to the required ionic strength by addition of the calculated amount of sodium perchlorate.

A measured volume of the perchloric acid solution was added to a known quantity of the sodium thiosulphate solution in a small beaker, and the pH was measured with a glass electrode and valve potentiometer. Several successive additions of small quantities of perchloric acid could sometimes be made before the opalescence showed that a significant amount of decomposition had occurred; more usually each mixture had to be made up afresh. All measurements were repeated five times; the observed values of the pH did not differ from the mean by more than 0·01 unit except in the most dilute solutions, where the scatter was about twice as great.

The electrodes were kept in distilled water between measurements and were well drained before each measurement. They were calibrated frequently with an M/20-solution of potassium hydrogen phthalate, whose pH was taken to be 4·01. All measurements were carried out in a thermostat kept at 25·00° ± 0·02° and the solutions were stored in the same thermostat.

A parallel series of experiments was made, in which the sodium thiosulphate solution was replaced by a solution of sodium perchlorate of the same ionic strength. The results of this series were used to calibrate the glass electrode in terms of the concentration of hydrogen ion in the mixed solution, thus avoiding errors due to the liquid-junction potential and enabling all calculations to be carried out with concentrations instead of activities.

Calculation of the Dissociation Constants of a Dibasic Acid.—Consider the solution obtained by mixing a volume V_A ml. of a solution of a fully dissociated acid of concentration A with V_B ml. of a solution of the salt of a weak dibasic acid of concentration B. Then, if we denote the concentrations of undissociated weak acid and singly and doubly dissociated anions by b_0, b_1, and b_2 respectively, and the hydrogen-ion concentration of the mixed solution by h, we have

$$V = V_A + V_B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Vh + 2V_BB = Vb_1 + 2Vb_2 + V_AA \quad \text{(electrical neutrality)} \quad . \quad . \quad . \quad . \quad (2)$$

$$V_BB = V(b_0 + b_1 + b_2) \quad \text{(conservation of weak acid anion)} \quad . \quad . \quad . \quad . \quad (3)$$

These can be combined with the expressions for the dissociation constants of the weak acid, *viz.*, $K_1 = b_1h/b_0$ and $K_2 = b_2h/b_1$, to give the relation

$$(V_AA - Vh)/V_BB = h(K_1 + 2h)/(h^2 + K_1h + K_1K_2)$$

Inversion of this equation gives

$$\frac{V_BB}{V_AA - Vh} = \frac{h^2 + K_1h + K_1K_2}{h(K_1 + 2h)} = \frac{K_1K_2 - h^2}{h(K_1 + 2h)} + 1 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and, putting

$$K' = (K_1K_2 - h^2)/(K_1 + 2h) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

we have

$$K' = V_AB/(V_AA - Vh) - 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

which depends only on known or measurable quantities.

Equation (5) can be rearranged to give

$$K_2 = K' + h(h + 2K')/K_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

When a sufficiently extensive range of measurements is available, the separate values of K_1 and K_2 can be obtained graphically from equation (7). In other cases, only K' can be calculated with accuracy, and it is assumed that K' is equal to K_2, the last term in equation (7) being negligible if $h \ll K'$.

Results.—Ionic strength, $I = 0{\cdot}094$. This concentration is the lowest which it is convenient to use, and the results are comparable with those of Yui and Hagisawa (*Bull. Inst. Phys. Chem. Res. Tokyo*, 1942, **21**, 5) and Denney and Monk (*Trans. Faraday Soc.*, 1951, **47**, 992) whose experiments were carried out under roughly the same conditions.

The measurements are collected and analysed in detail in Table 1. Only abbreviated Tables will be given for the results at other ionic strengths, as the details of the analysis are the same in each case. The value of K', the apparent dissociation constant, falls as the hydrogen-ion concentration rises, in accord with equation (5). The results lead to the values $K_1 = 0{\cdot}52$, $K_2 = 0{\cdot}0573$, which become $K = 0{\cdot}65$ and $K = 0{\cdot}0517$, respectively, when corrected for the effect of sodium in forming $NaS_2O_3^-$.

TABLE 1.

$10^4[H^+]$	Total thio-sulphate	Total Na ion	$10^4[H^+]$ con-sumed	K' (eqn. 5)	$[S_2O_3^-]$	$10^4 \times [NaS_2O_3]$	$[Na^+]$	$[HS_2O_3^-]$	K', corr.	I
15·4	0·0325	0·0650	9·0	0·0540	0·0285	30·8	0·0619	0·00090	0·0487	0·0959
24·9	0·0320	0·0640	13·6	0·0560	0·0277	29·5	0·0610	0·00136	0·0507	0·0956
40·9	0·0313	0·0626	21·9	0·0544	0·0263	27·5	0·0598	0·00219	0·0491	0·0952
60·4	0·0303	0·0606	30·5	0·0540	0·0248	25·1	0·0581	0·00305	0·0491	0·0944
90·0	0·0290	0·0580	40·3	0·0558	0·0228	22·2	0·0358	0·00403	0·0509	0·0938
135	0·0270	0·0540	54	0·0540	0·0198	18·1	0·0522	0·0054	0·0494	0·0927
220	0·0238	0·0476	66	0·0513	0·0159	12·9	0·0463	0·0066	0·0530	0·0921
258	0·0222	0·0444	75	0·0506	0·0137	10·4	0·0434	0·0075	0·0471	0·0914
350	0·0191	0·0382	79	0·0497	0·0105	6·9	0·0375	0·0079	0·0465	0·0916
420	0·0167	0·0333	80	0·0458	0·0082	4·7	0·0328	0·0080	0·0430	0·0915
527	0·0133	0·0267	73	0·0433	0·0057	2·7	0·0264	0·0073	0·0411	0·0924

This Table calls for certain comments. It is not correct, even in solutions as dilute as these, to ignore the effects of undissociated thiosulphuric acid, and to equate the hydrogen

ions consumed to the $HS_2O_3^-$ formed, as has been done here. The correction for the formation of $NaS_2O_3^-$ was made by using a value $K_{NaS_2O_3^-} = 0{\cdot}57$. This value, although obtained by application of Davies's activity relation (see below), is probably fairly accurate, as the experimental work upon which it is based was carried out at an ionic strength of about 0·11, and the same relation used to extrapolate to zero ionic strength. The mean value of the ionic strength had been taken as 0·094.

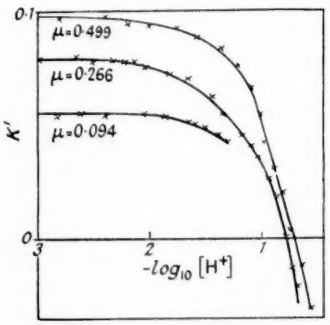
Ionic strengths $I = 0{\cdot}27$ *and* 0·50. The results at these ionic strengths followed the same pattern as those at the lower ionic strength, except that the more concentrated solutions enabled measurements to be made under slightly more acid conditions, and the value of K' could be followed much further, until it became negative. The measurements are shown graphically in the Figure. The results are in agreement with the values for the two dissociation constants shown below. These values have not been corrected for the effect of $NaS_2O_3^-$.

I	K_1	K_2	I	K_1	K_2
0·27	0·35	0·0816	0·50	0·45	0·0970

Ionic strengths $I = 0{\cdot}78$ *and* 0·91. The measurements at these strengths were hampered by rapid precipitation of sulphur, and the accessible range of hydrogen-ion concentration was small. It was possible to make sufficient measurements to determine the values of both dissociation constants, but the accuracy was lower than in the previous experiments. A number of results are collected in Table 2.

TABLE 2.

$[H^+]$	Total thiosulphate	$[H^+]$ consumed	Total Na	K'	I
0·00589	0·0909	0·00363	1·000	0·141	0·916
0·00891	0·0869	0·0047	1·000	0·147	0·914
0·0138	0·0800	0·0072	0·999	0·141	0·912
0·0155	0·0769	0·0087	0·998	0·136	0·910
0·0407	0·0500	0·0117	0·996	0·133	0·906
0·0515	0·0333	0·0723	0·994	0·098	0·908
0·0190	0·278	0·0400	0·640	0·113	0·784
0·0299	0·256	0·0518	0·619	0·118	0·782
0·0400	0·239	0·0611	0·627	0·116	0·782
0·0504	0·222	0·0676	0·641	0·115	0·780
0·0648	0·278	0·112	0·556	0·096	0·777
0·102	0·256	0·193	0·512	0·082	0·778
0·135	0·238	0·171	0·476	0·057	0·776
0·162	0·222	0·191	0·444	0·026	0·779
0·231	0·055	0·064	0·348	0·031	0·781



The concentration of sodium ion in the solutions studied is so high that it is essential to take into account the ion $NaS_2O_3^-$. The dissociation constant of this ion has been determined by Denney and Monk (*loc. cit.*), but their results were obtained at relatively low ionic strengths, and considerable uncertainly must occur in any extrapolation to the ionic strength used in the present work.

Davies (*J.*, 1938, 2093) has pointed out that the mean activity coefficients of many electrolytes can be represented over a considerable range of ionic strengths by the equation

$$\log \gamma_{\pm} = 0{\cdot}505 Z_1 Z_2 \left\{ \frac{\sqrt{I}}{1+\sqrt{I}} - 0{\cdot}2I \right\} = 0{\cdot}505 Z_1 Z_2 \, f(I)$$

where Z_1, Z_2 are the charges of the ions and I is the ionic strength. Davies also suggested that this relation was generally applicable, provided that the ionic strength was not too great. This equation, applied to the dissociation of $NaS_2O_3^-$, gives for the dissociation constant at an ionic strength of I: $\log K_1 = \log K_0 + 2{\cdot}02 f(I)$. The dissociation constant of $NaS_2O_3^-$ has been calculated by this equation for each ionic strength, and the dissociation constants thus obtained have been used to correct the observed dissociation constants of $HS_2O_3^-$ for the errors due to the formation of $NaS_2O_3^-$.

The second dissociation constant of thiosulphuric acid is shown by equation (7) to be

the limit of K' as the hydrogen-ion concentration tends to zero. Inserting this in equation (6), we obtain

$$K_2 = \underset{h \to 0}{\text{Lt}}\ (K') = \underset{h \to 0}{\text{Lt}} \left\{ \frac{V_B B h}{V_A A - V h} - h \right\}$$

In the limit, $V_A = 0$ and $V = V_B$. The correction for formation of $NaS_2O_3^-$ in the solution is made by multiplying the observed value of K_2 by the fraction of thiosulphate in the solution of sodium thiosulphate which is in the free state, *i.e.*,

$$K_2 = \left[\underset{h \to 0}{\text{Lt}}\ (K') \right] \times \left[\frac{[S_2O_3^{--}]}{[S_2O_3^{--}] + [NaS_2O_3^-]} \right]$$

The latter factor can be computed from the dissociation constant of the ion $NaS_2O_3^-$. It is necessary to use successive approximations, since the ionic strength involves a knowledge of the concentration of $NaS_2O_3^-$ present. The computed dissociation constants of $NaS_2O_3^-$ at the various ionic strengths are given in Table 3, together with the observed and corrected dissociation constants of $HS_2O_3^-$ at each ionic strength and the value at zero ionic strength calculated from each result by Davies's equation.

TABLE 3.

Ionic strength		0	0·094	0·266	0·949	0·775	0·910
$K_{NaS_2O_3^-}$		0·21	0·57	0·79	0·87	0·90	0·90
$K_{HS_2O_3^-}$	obs.	—	0·0573	0·0816	0·0970	0·143	0·118
	corr.	—	0·0517	0·0673	0·0776	0·0788	0·0759
	$I = 0$	0·0184	0·0191	0·0179	0·0187	0·0187	0·0177

The value of K_1 is obtained from the hydrogen-ion concentration at which K' is zero. At this point K_1K_2 is equal to the square of the hydrogen-ion concentration, and the concentrations of sodium ion and free thiosulphate ion are so small that the concentration of $NaS_2O_3^-$ may be neglected. The values of K_1 obtained in this way are collected in Table 4, together with the values at zero ionic strength obtained by applying Davies's formula.

TABLE 4.

Ionic strength	0	0·094	0·266	0·499	0·775	0·910
Critical hydrogen-ion concentration ...	—	0·142	0·169	0·209	0·197	0·185
K_1	—	0·53	0·49	0·45	0·49	0·45
K_1 ($I = 0$)	0·25	0·32	0·25	0·22	0·24	0·22

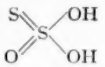
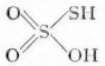
Discussion.—The use of an empirical activity equation to correlate equilibrium constants at different ionic strengths is only valid if it is known that the equation applies in the region studied. Davies's equation was proposed to cover the range $I = 0$ to $I = 0{\cdot}1$, and the results obtained in this work lies well outside this range. If the results of Davies and Righellato (*Trans. Faraday Soc.*, 1930, **26**, 592) for the conductivity of potassium sulphate are examined, it is found that the empirical equation expresses these measurements even at 0·2M ($I = 0{\cdot}6$). From this, it appears that any errors introduced by the use of this equation will be less than the errors of experiment. Furthermore, the errors thus introduced are likely to be the same in the dissociation constants of both $HS_2O_3^-$ and $NaS_2O_3^-$, and will tend to cancel, particularly in those experiments where the corrections for the effect of sodium are important. The use of this empirical equation brings the varied results at different ionic strengths to a common value and, as the equation may reasonably be expected to apply at the lowest ionic strength studied, it can be taken to apply throughout the range of the experiments.

The value of the second dissociation constant now obtained is somewhat lower than the values obtained by previous workers (Denney and Monk, Yui and Hagisawa, *locc. cit.*) and the difference cannot be entirely ascribed to the use of perchloric acid instead of hydrochloric acid. A more probable explanation of the difference lies in the method by which the hydrogen-ion concentration is calculated. The use of activity coefficients predicted by general formulæ is always open to criticism, particularly so when, as in the present work, the numerical result is very sensitive to slight changes in the value of the activity coefficient. The method of calibration used in the present work avoids this source of

error, and at the same time reduces to a minimum the difference between the liquid-junction potentials in the calibrating and experimental cells.

The structure of the thiosulphate ion has frequently been compared to that of the sulphate ion, and Jellinek (*loc. cit.*) on these grounds estimated the first dissociation constant of thiosulphuric acid. It is instructive to compare the values for the dissociation constants of thiosulphuric acid obtained here with those measured or estimated for sulphuric acid.

The comparison of the second dissociation constants shows that $HS_2O_3^-$ ($K_2 = 0{\cdot}018$ at 25°) is a slightly stronger acid than is HSO_4^- ($K_2 = 0{\cdot}012$ at 25°; Hamer, *J. Amer. Chem. Soc.*, 1936, **58**, 2126) in agreement with many observations on salts and complex ions of the two acids. There is no such agreement between the first dissociation constants; indeed, the value obtained in this paper contravenes all the relations observed between first and second dissociation constants of acids. A dibasic acid with two equivalent ionising groups should have a first and second dissociation constant differing by a factor of 10^5 (Pauling, " General Chemistry," 1947, p. 394) or $10^{5{\cdot}1}$ (MacGowan, *Chem. and Ind.*, 1948, 632), so that sulphuric and thiosulphuric acids should have a dissociation constant of about 1000, and the curvature to be seen in the figure should be unobservable. The classification adopted by Ricci (*J. Amer. Chem. Soc.*, 1948, **70**, 109) would indicate a much smaller value, but, as he remarks, the group into which sulphuric acid falls is not sufficiently homogeneous to enable any conclusion to be drawn.

(I)   (II)

Two structures have been proposed for thiosulphuric acid—the symmetric structure (I) in which the ionisable hydrogen are both attached to oxygen atoms, and the asymmetric structure (II) in which one hydrogen is attached to the sulphur atom. The estimation of the difference between the dissociation constants outlined above is only valid when the ionisable hydrogen atoms are equivalent, *i.e.*, for the structure (I). The asymmetric formula is strongly supported by studies on the formation of organic thiosulphates from thiols and chlorosulphonic acid (Mellor, " Inorganic Chemistry ") and the strongly coloured ferric thiosulphate complex ion is typical of the complexes formed between Fe^{3+} and compounds containing the thiol group. The physical evidence is not decisive, though the S–S internuclear distance of 2·1 Å (Gupta and Guha, *Proc. Nat. Inst. Sci. India*, 1941, **7**, 267) suggests a single covalent bond.

The dissociation constants of phenol and thiophenol have been measured under similar conditions (Fletcher, *J. Amer. Chem. Soc.*, 1946, **68**, 2726) and thiophenol is the stronger acid by 3·3 units of pK. If thiosulphuric acid has the asymmetric formula, the usual empirical rules will not apply, since the two ionisable hydrogen atoms are not equivalent, but the S–H bond should be the first to break. The resulting ion closely resembles the HSO_4^- ion, and may be compared with it.

In the absence of comparable measurements on sulphuric acid by the technique used here, the possibility that the abnormally low first dissociation constant of thiosulphuric acid is fictitious cannot be completely ruled out, but the consistency of the results from widely different conditions of experiment strongly suggests that the value reported here is of the correct order of magnitude, and the explanation of the low value must be sought in the detailed structure of thiosulphuric acid itself.

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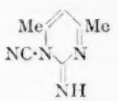
356. *2-Cyanoamino-4 : 6-dimethylpyrimidine and Complexes formed by Pyrimidines with Urea and Related Compounds.*

By S. Birtwell.

2-Cyanoamino-4 : 6-dimethylpyrimidine, previously designated 1-cyano-1 : 2-dihydro-2-imino-4 : 6-dimethylpyrimidine, gives on acid hydrolysis first 4 : 6-dimethyl-2-ureidopyrimidine and then a 1 : 1 molecular complex of 2-hydroxy-4 : 6-dimethylpyrimidine and urea. This complex was incorrectly formulated by earlier workers. Molecular complexes are also formed between a number of other pyrimidines and urea. Compounds related to urea such as cyanoguanidine, biuret, and thiourea may replace urea in these complexes, whose structures are discussed.

The reactions between arylamines and 2-cyanoamino- and 2-ureido-4 : 6-dimethylpyrimidine are described.

To the product of reaction between acetylacetone and cyanoguanidine, Hale and Vibrans (*J. Amer. Chem. Soc.*, 1918, **40**, 1060) assigned structure (I). Nevertheless, in an attempt to prepare compound (III) by addition of *p*-chloroaniline (as its hydrochloride) to (I), 2-*p*-chlorophenylguanidino-4 : 6-dimethylpyrimidine (IV) (Cliffe, Curd, Rose, and Scott, *J.*, 1948, 574) was isolated as sole product. It appears, therefore, that the correct structure is 2-cyanoamino-4 : 6-dimethylpyrimidine (II), and this has been confirmed by an unambiguous synthesis from 2-chloro-4 : 6-dimethylpyrimidine and sodium cyanamide. The condensation of cyanoguanidine with a β-diketone, therefore, is similar to its reactions with β-keto-esters (Pohl, *J. pr. Chem.*, 1908, **77**, 533; Crowther, Curd, and Rose, *J.*, 1948, 586) and malonic ester (Merck, D.R.-P. 158,591) which also give 2-cyanoaminopyrimidines.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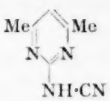
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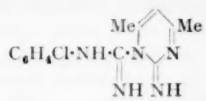
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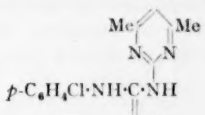
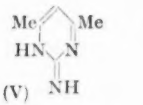

(IV)

Several attempts to prepare (I) by reaction of 2-amino-4 : 6-dimethylpyrimidine (VI) with bromine and potassium cyanide or with cyanogen bromide were unsuccessful.

The crux of the argument advanced by Hale and Vibrans (*loc. cit.*) in support of structure (I) lay in the formation, on dilute acid hydrolysis, of 1 : 2-dihydro-2-imino-4 : 6-dimethylpyrimidine (V) (as its monohydrate), which, it was claimed, was different from the 2-amino-4 : 6-dimethylpyrimidine (VI) of A. and C. Combes (*Bull. Soc. chim.*, 1892, **7**, 788). Such a theory is untenable now, so the product of hydrolysis of (I) has been re-examined; it has been shown to be a 1 : 1 complex of 2-hydroxy-4 : 6-dimethylpyrimidine and urea, being readily obtained by mere crystallisation of equimolecular proportions of urea and the pyrimidine from alcohol; it was first prepared by Evans (*J. pr. Chem.*, 1892, **46**, 352; 1893, **48**, 489) and A. and C. Combes (*Bull. Soc. chim.*, 1893, **7**, 791) from acetylacetone and excess of urea. These authors, who called the substance "diurimidoacetylacetone," suggested that it was 2 : 4-biscarbamyliminopentane (VII), whereas de Haan (*Rec. Trav. chim.*, 1908, **27**, 162) and Hale (*J. Amer. Chem. Soc.*, 1914, **36**, 104) regarded it as 1 : 2 : 3 : 4-tetrahydro-4 : 6-dimethyl-4-ureido-2-pyrimidone (VIII). Nevertheless, de Haan's observations (*loc. cit.*), and the identity between the ultra-violet absorption spectrum of this substance and the curve obtained by superimposing the spectrum of 2-hydroxy-4 : 6-dimethylpyrimidine on that of urea, suggest that it is a molecular complex. This has been confirmed by conversion into the sodium salt of 2-hydroxy-4 : 6-dimethylpyrimidine, and into dixanthylurea. Boarland and McOmie (*J.*, 1952, 3722) have recently shown that the sulphur analogue of (VII) ("dithiourimidoacetylacetone") is also, in fact, a molecular complex of thiourea and 2-mercapto-4 : 6-dimethylpyrimidine.

4 : 6-Dimethyl-2-ureidopyrimidine is readily obtained from (II) by the action of cold concentrated sulphuric acid, or boiling dilute sulphuric acid (2 min.). The same compound may be synthesised in small yield from (VI) by reaction with urethane [cf. Bamberger (*Ber.*, 1887, **20**, 69) for a similar preparation of guanylurea]. 4 : 6-Dimethyl-2-ureidopyrimidine gives the molecular complex described above when boiled for 1 hr. with dilute sulphuric acid. By fusing it with *p*-chloroaniline hydrochloride or sulphanilamide hydrochloride at 150—160°, one obtains the 2-*p*-chlorophenylureido- or the 2-*p*-sulphamylphenylureido-derivative, respectively. The free amines are much less satisfactory for this purpose.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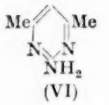
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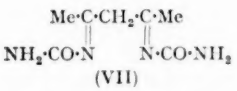
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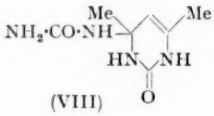

(VIII)

The reaction between (II) and 2 mols. of sulphanilamide at 170° has been described as giving 4 : 6-dimethyl-2-sulphanilamidopyrimidine and sulphanilylguanidine (B.P. 635,876). Despite numerous attempts it has not been possible to substantiate this result. However, equimolecular proportions of sulphanilamide hydrochloride and (II) combine at 78° in alcohol to give *N*-2-(4 : 6-dimethylpyrimidyl)-*N'*-*p*-sulphamylphenylguanidine, whereas sulphanilamide itself when dissolved with (II) in either boiling alcohol or water gives a 1 : 1 complex. It may be conclusively demonstrated that this substance *is* a complex by diazotisation and coupling to give *p*-sulphamylphenylazo-β-naphthol and by comparison of its ultra-violet absorption spectrum with those of sulphanilamide and (II) determined separately. The curves are additive, and isosbestic points are shown at 212, 261, and 290 mμ (in water).

Arising out of this investigation, a number of pyrimidines were examined for the property of complex formation with urea, and urea-like compounds. Among the complexes observed was that between urea and 2-amino-4 : 6-dimethylpyrimidine, and those of thiourea with 2-amino- and 2-mercapto-4 : 6-dimethylpyrimidine which have since been reported (Bray, Lake, and Thorpe, *Biochem. J.*, 1951, **48**, 400; Boarland and McOmie, *loc. cit.*). These examples and the urea–2-hydroxy-4 : 6-dimethylpyrimidine complex described above are particular cases of a phenomenon which is now shown to be quite general for these chemical types.

Our results, which are illustrative rather than exhaustive, are set out in Tables 1, 2, and 3.

TABLE 1. *Equimolecular complexes of some dimethylpyrimidines and urea.**

Dimethyl-pyrimidine	Solvent	M. p.†	Formula	Analytical data Found, % C	H	N	Reqd., % C	H	N	Notes ‡
2-Hydroxy-4 : 6-	98% EtOH	203° †	$C_6H_8ON_2,CH_4ON_2$	46·1	6·5	30·2	45·7	6·5	30·4	A
2-Amino-4 : 6- ...	,,	192—193 †	$C_6H_9N_3,CH_4ON_2$	45·9	7·1	38·0	46·0	7·1	38·2	A
2-Mercapto-4 : 6-	95% ,,	199—200 †	$C_6H_8N_2S,CH_4ON_2$	42·1	6·2	27·8	42·0	6·0	28·0	A
4-Hydroxy-2 : 6-	98% ,,	160—162	$C_6H_8ON_2,CH_4ON_2$	46·1	6·6	29·8	45·7	6·5	30·4	B
4-Amino-2 : 6- ...	,, ,,	153—155	$C_6H_9N_3,CH_4ON_2$	46·0	7·4	38·0	46·0	7·1	38·2	B, C

* The constituents were mixed in equimolar proportion in solution.
† M. p.s designated thus are with decomp.
‡ A. Composition and m. p. unchanged on recrystallisation.
B. Not recrystallised.
C. Complex rather soluble in EtOH, so crystallisation induced by concentration.

The following pyrimidines, in alcoholic solution, failed to give complexes with urea : 2 : 4 : 6-trimethyl-, 4-ethoxy-2 : 6-dimethyl-, 4 : 6-dimethyl-2-sulphanilamido-, 4 : 6-dimethoxy-2-sulphanilamido-. 4-Methyl*iso*cytosine crystallised with some urea, but not in stoicheiometric proportion. Benzamide did not give a complex when substituted for urea.

The 1 : 1 complexes shown in Table 1 were the most easily prepared, being generally of low solubility in alcohol, of high m. p., and stable to recrystallisation. In these respects

the complexes with 4-hydroxy- and with 4-amino-2 : 6-dimethylpyrimidine were less stable than with the isomeric 2-hydroxy- and 2-amino-compounds.

The complexes in Table 2 crystallised with urea in molecular ratios other than unity. 2-Cyanoamino- and 2-ureido-4 : 6-dimethylpyrimidine formed crystalline complexes only from solutions containing excess of urea and gave the pure (less soluble) pyrimidine itself on recrystallisation. The complex with 4-methyluracil crystallised from aqueous alcohol containing excess of urea only very slowly during several days. On the other hand, excess of the pyrimidine was used in the cases of the more soluble 2-ethoxy- and 2-methylthio-pyrimidines. It is also noteworthy that different solvents may lead to complexes of different molecular ratio.

TABLE 2. *Complexes of dimethylpyrimidines and urea in other than equimolecular ratio.*

4 : 6-Dimethyl-pyrimidine	Solvent	Molar ratio, urea : pyrimidine in soln.	M. p.*	Found, % C	H	N	Formula	Reqd., % C	H	N	Notes †
2-Cyano-amino-	MeOH	7 : 1	184—185°	43·4	6·0	41·1	$2C_7H_8N_4,3CH_4ON_2$	42·7	5·9	41·0	A
2-Ureido-	,,	11 : 2	188—189	38·2	6·4	38·6	$C_7H_{10}ON_4,2CH_4ON_2$	37·8	6·3	39·1	B
2-Ethoxy-	98% EtOH	1 : 1	134—136	40·1	7·5	33·8	$C_8H_{12}ON_2,3CH_4ON_2$	39·8	7·2	33·7	C
2-Ethoxy-	MeOH	1 : 4	134—135	43·3	7·1	31·2	$C_8H_{12}ON_2,2CH_4ON_2$	44·1	7·3	30·9	D
2-Methylthio-	,,	10 : 3	147—148	39·7	6·7	30·9	$C_7H_{10}SN_2,2CH_4ON_2$	39·4	6·6	30·6	E
(4-Methyl-uracil)	80% Aq. EtOH	10 : 1	301	42·2	4·6	28·0	$2C_5H_6O_2N_2,CH_4ON_2$	42·3	5·1	27·0	F

* All substances showed shrinkage before melting, except the last, which melted with decomp.

† A. After two recrystallisations from methanol, the original pyrimidine was obtained, m. p. and mixed m. p. 234—235°.
B. The complex not recrystallised.
C. M. p. and analysis refer to material after recrystallisation from absolute alcohol, in which it was rather soluble.
D. A very small volume of solvent was used. The complex was not recrystallised.
E. Sufficient methanol was used to obtain complete solution at the boil. The complex was not recrystallised.
F. The complex crystallised very slowly (several days) in low yield.

TABLE 3. *Equimolecular complexes of 2-hydroxy-4 : 6-dimethylpyrimidine with compounds related to urea.**

Urea-like compound	M. p.	Found, % C	H	N	Formula	Reqd., % C	H	N	Notes †
Cyanoguanidine	220—222°	42·5	6·6	38·1	$C_6H_8ON_2,C_2H_3N_4,H_2O$	42·5	6·2	37·2	A, B
Biuret	219—221	42·4	5·9	32·5	$C_6H_8ON_2,C_2H_5O_2N_3$	42·3	5·7	30·8	B
Thiourea	203—204	41·4	6·5	28·4	$C_6H_8ON_2,CH_4N_2S$	42·0	6·0	28·0	B

* Equimolar proportions, dissolved in 95% EtOH, were mixed.

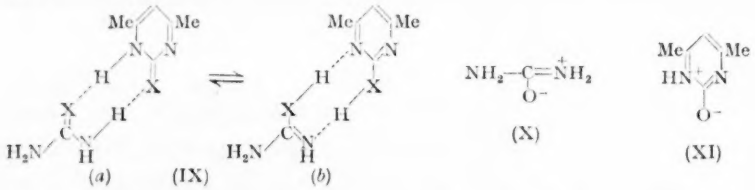
† A. Complex obtained as monohydrate. B. Complexes were not recrystallised.

In Table 3 are listed the complexes between 2-hydroxy-4 : 6-dimethylpyrimidine and urea-like substances. They closely resemble the 1 : 1 complexes formed by urea.

Although any discussion of the structure of these complexes can only be very speculative, it is probable that the compounds are associated by hydrogen bonding both in the crystal and in solution. This association may be especially powerful owing to cyclic structures being involved; *e.g.*, the complexes of Table 1 may well be represented by (IX, *a* and *b*; X = O, S, NH).

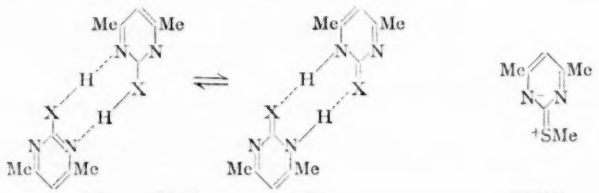
In urea, and the pyrimidines of Table 1, bipolar mesomeric forms such as (X) and (XI) may be expected to make large contributions to their respective structures, and would greatly favour hydrogen-bond formation (which is regarded as largely electrostatic in character : see Symposium on the Hydrogen Bond, Royal Institute of Chemistry, 1949). It is necessary to point out, however, that Marshall and Walker (*J.*, 1951, 1004), on the

basis of the observed similarity in the spectra of 2-hydroxy-4 : 6-dimethylpyrimidine (which exists in the dihydro-keto-form) and its cation, concluded that the canonical form (XI) makes little contribution to the structure. In this, however, they failed to take into account that an equilibrium will exist in solution between the tautomeric hydroxy- and dihydro-keto-forms, a point which has been stressed by Brown and Short (*J.*, 1953, 331). It is the author's opinion, also, that pyrimidines of this type constitute a further example of mesohydric tautomerism (Hunter, *J.*, 1945, 806), protonic resonance occurring in such associated structures as (XII, *a* and *b*)—hence the impossibility of isolating the different tautomeric forms. Equilibrium between the two structures would be attained almost instantaneously and ultra-violet absorption spectra would reveal only the predominating, more stable one.



(*a*) (IX) (*b*) (X) (XI)

Some of the pyrimidines in Table 2 may receive important contributions to their structure from canonical forms similar to (XI). In others, a bipolar mesomeric structure such as (XIII) has been postulated (Boarland and McOmie, *loc. cit.*) and might be held equally to favour complex formation, although of a different type.



(*a*) (XII) (*b*) (XIII)

Ionic forms can make only slight contributions to the structures of 2 : 4 : 6-trimethylpyrimidine and to 4-ethoxy-2 : 6-dimethylpyrimidine, and this may be the reason for their failure to form complexes. A similar explanation may serve for the inability of benzamide to replace urea. On the other hand, some pyrimidines whose structures must receive large contributions from bipolar forms have not given complexes, and one can only conclude that the many requirements for crystal formation over and above mere intermolecular association are not fulfilled in these cases.

Experimental

M. p.s are uncorrected.

2-*Cyanoamino*-4 : 6-*dimethylpyrimidine* (II).—(*a*) Prepared by the method of Hale and Vibrans (*loc. cit.*) from cyanoguanidine (80 g.), acetylacetone (134 g.), and 2N-sodium hydroxide (40 c.c.) in water (1 l.), at 95—100°, this *pyrimidine* (contrast structure assigned by Hale and Vibrans, *loc. cit.*) was obtained as a white powder (54 g.; m. p. 230—231°) which crystallised from ethanol in small, cream-coloured prisms, m. p. 231—232° after darkening (Found: C, 56·8; H, 5·0; N, 37·7. $C_7H_8N_4$ requires C, 56·8; H, 5·4; N, 37·8%).

(*b*) 2-Chloro-4 : 6-dimethylpyrimidine (28·5 g.) and monosodium cyanamide (13·0 g.) in sodium-dried ethanol (600 c.c.) were heated under reflux with stirring for 20 hr., whereupon sodium chloride separated gradually. A little water was added and carbon dioxide was passed through the cooled solution for 1 hr. Insoluble material was filtered off, and the filtrate was evaporated under reduced pressure, leaving a semi-solid residue, a portion of which dissolved on treatment with acetone (50 c.c.). The crystalline solid which remained was filtered off,

stirred with water, and acidified (faint reaction to Congo-red) with dilute hydrochloric acid. 2-Cyanoamino-4 : 6-dimethylpyrimidine (II) was precipitated and crystallised from methanol, being obtained as almost colourless needles (1·5 g.), m. p. 233—234°, not depressed on admixture with material prepared by method (*a*).

Reactions of 2-*Cyanoamino*-4 : 6-*dimethylpyrimidine with Amines.*—(a) *With* p-*chloroaniline hydrochloride.* *p*-Chloroaniline hydrochloride (4·1 g.) and (II) (3·3 g.) were heated under reflux in ethanol for 4 hr. After being cooled and clarified, the solution was treated with 2N-sodium hydroxide (20 c.c.); 2-*p*-chlorophenylguanidino-4 : 6-dimethylpyrimidine (IV) (5·0 g.) crystallised, and was collected, washed with aqueous methanol, and dried at 60—70°. It had m. p. 206—207°, not depressed by admixture with material prepared from *p*-chlorophenyldiguanide and acetylacetone (Cliffe, Curd, Rose, and Scott, *loc. cit.*).

(b) *With sulphanilamide hydrochloride.* In a similar manner (II) (3·3 g.) and sulphanilamide hydrochloride (5·0 g.) in alcohol (50 c.c.) were heated under reflux for 7½ hr. 4 : 6-*Dimethyl*-2-p-*sulphamylphenylguanidinopyrimidine* (4·0 g.), m. p. 203—205°, crystallised on cooling. It was recrystallised from alcohol (carbon), and obtained as colourless prisms, m. p. 235° (decomp.) (Found : C, 49·1; H, 5·2; N, 26·1. $C_{13}H_{16}O_2N_6S$ requires C, 48·7; H, 5·0; N, 26·2%). The hydrochloride was sparingly soluble in cold dilute hydrochloric acid, but dissolved on warming. It was unaffected by nitrous acid.

(c) *With sulphanilamide.* (i) A mixture of (II) (3·0 g.), sulphanilamide (3·5 g.), and alcohol (50 c.c.) was boiled for 3 hr. At no time was a clear solution obtained. After being cooled, the 1 : 1 *complex* of (II) and sulphanilamide was filtered off, washed with alcohol, and dried at 100° (5·0 g.; m. p. 189—191°). It crystallised from water (charcoal) in glistening needles (4·3 g.; m. p. 190—191°, varying with rate of heating) (Found : C, 48·7; H, 5·2; N, 25·8. $C_{13}H_{16}O_2N_6S$ requires C, 48·7; H, 5·0; N, 26·2%), soluble in both dilute acids and dilute caustic alkalis.

A portion was diazotised and coupled with β-naphthol. After being twice recrystallised from nitrobenzene, the product had m. p. 259—261°, and mixed m. p. 259—261° with material similarly prepared from sulphanilamide and β-naphthol (Found : C, 58·4; H, 4·1; N, 12·6. Calc. for $C_{16}H_{13}O_3N_3S$: C, 58·7; H, 4·0; N, 12·8%).

(ii) Sulphanilamide (1·8 g.) was dissolved in boiling water (50 c.c.), and the cyanoaminopyrimidine (II) (1·5 g.) added. Dissolution of this normally sparingly soluble material was instantaneous. The solution was filtered and cooled immediately, whereupon the molecular compound, m. p. 190—191°, crystallised. It was identical with that prepared by method (i) above.

Hydrolysis of 2-*Cyanoamino*-4 : 6-*dimethylpyrimidine* (II).—A solution of the pyrimidine (II) (4·0 g.) in dilute sulphuric acid (conc. acid, 16 c.c.; water, 80 c.c.) was heated under reflux for 3 hr. By continuing according to Hale and Vibrans (*loc. cit.*), a molecular complex of 2-hydroxy-4 : 6-dimethylpyrimidine and urea (Table 1) was obtained, crystallising from absolute alcohol in pale yellow plates, m. p. and mixed m. p. with a specimen prepared from the two components, 203—204° (decomp.) (Loss at 140° during 2½ hr. : 0·4%).

Isolation of Components from Molecular Complex of 2-*Hydroxy*-4 : 6-*dimethylpyrimidine and Urea.*—(*a*) The complex was suspended in warm alcohol, and alcoholic sodium ethoxide added until the solution gave an alkaline reaction on moist Titan-yellow paper. The sodium salt of 2-hydroxy-4 : 6-dimethylpyrimidine separated, and was filtered off and washed well with alcohol. It was again suspended in alcohol and a stream of carbon dioxide was bubbled through the mixture. The gelatinous precipitate of sodium carbonate was filtered off, and the filtrate was concentrated; yellow crystals of 2-hydroxy-4 : 6-dimethylpyrimidine dihydrate crystallised, m. p. and mixed m. p. 196—198°.

(*b*) The complex (0·25 g.) in 50% acetic acid (20 c.c.) was treated in the cold with a solution of xanthhydrol (0·5 g.) in alcohol (12·5 c.c.). A precipitate slowly formed and was filtered off after 1½ hr. It was washed with 50% alcohol, dried at 90—100°, and then had m. p. 278—279° (decomp.), not depressed on admixture with an authentic specimen of dixanthylurea.

4 : 6-*Dimethyl*-2-*ureidopyrimidine.*—(*a*) The pyrimidine (II) (20·0 g.) was added gradually to concentrated sulphuric acid (100 c.c.) at 10—20°, and the mixture stirred at room temperature to complete dissolution of the solid. With good stirring, ice (100 g.) was introduced gradually, the temperature being kept about 30°. When the acid solution was poured into concentrated sodium hydroxide liquor (NaOH, 160 g.; water, 500 c.c.) and cooled below 30° by addition of ice, 4 : 6-dimethyl-2-ureidopyrimidine was precipitated. This was filtered off, washed well with water, dried at 90—100°, and crystallised from alcohol, affording 12 g. (m. p. and mixed m. p. with material prepared from 2-amino-4 : 6-dimethylpyrimidine, 207—208°).

(*b*) The cyanoaminopyrimidine (II) (6·0 g.) was dissolved in 6N-sulphuric acid (150 c.c.), heated to boiling (8 min.), boiled for a further 2 min., and poured into a solution of 4N-sodium hydroxide (180 c.c.) and ice (300 g.), giving 4 : 6-dimethyl-2-ureidopyrimidine (5·4 g.; m. p. 211°).

(*c*) Urethane (10 g.) and 2-amino-4 : 6-dimethylpyrimidine (VI) (5 g.) were heated for 1 hr. at 190—200° with slow distillation of urethane (and ethanol). The resulting mixture was cooled slightly and diluted with aqueous alcohol. An insoluble by-product was filtered off while still warm; 4 : 6-*dimethyl*-2-*ureidopyrimidine* separated from the cooled filtrates. After successive crystallisations from alcohol (twice) and acetone, it had m. p. 209° and was identical with material obtained in the hydrolysis experiments (*a* and *b*, above) (Found : C, 50·5; H, 6·0; N, 33·0. $C_7H_{10}ON_4$ requires C, 50·6; H, 6·0; N, 33·7%).

Hydrolysis of 4 : 6-*dimethyl*-2-*ureidopyrimidine.* A solution of the ureidopyrimidine (2·0 g.) was hydrolysed with sulphuric acid as described for the cyanoamino-compound. The molecular complex of urea and 2-hydroxy-4 : 6-dimethylpyrimidine (0·9 g.; m. p. 203—204°, decomp.) was again obtained.

Reactions of 4 : 6-*Dimethyl*-2-*ureidopyrimidine with Amines.*—4 : 6-*Dimethyl*-2-p-*sulphamylphenylureidopyrimidine.* Sulphanilamide hydrochloride (2·1 g.) and 4 : 6-dimethyl-2-ureidopyrimidine (1·7 g.) were ground together and heated slowly in an oil-bath. At 150° a slightly exothermic reaction occurred, the temperature rose to 165°, and the contents of the tube solidified. After a further 10 min. at 150—160°, the product was cooled and ground. It was then boiled with water acidified with a few drops of hydrochloric acid. The insoluble 4 : 6-*dimethyl*-2-p-*sulphamylphenylureidopyrimidine* was filtered off, washed well, and dried at 100° (2·3 g.; m. p. 260—264°, decomp.). After recrystallisation from 2-ethoxyethanol, it had m. p. 265° (decomp.) (Found : C, 48·9; H, 4·6; N, 22·0. $C_{13}H_{15}O_3N_5S$ requires C, 48·6; H, 4·7; N, 21·8%). The absence of a free amino-group in this material was demonstrated by attempted diazotisation (nitrosylsulphuric acid method) which failed.

2-p-*Chlorophenylureido*-4 : 6-*dimethylpyrimidine.* Similarly, *p*-chloroaniline hydrochloride (1 g.) and 4 : 6-dimethyl-2-ureidopyrimidine (1 g.), ground together and heated to 160° for ½ hr., gave 2-p-*chlorophenylureido*-4 : 6-*dimethylpyrimidine* (1·3 g.), m. p. 206—209°, crystallising from butanol in long, colourless, felted needles, m. p. 211—212° (Found : C, 57·1; H, 4·9; N, 19·6. $C_{13}H_{13}ON_4Cl$ requires C, 56·4; H, 4·7; N, 20·2%).

Equimolecular Complexes of Pyrimidines with Urea (*see Table* 1).—A solution of the pyrimidine (0·01 g.-mol.) in the solvent (10 c.c.) was mixed with a solution of urea (0·01 g.-mol.) in the same solvent (10 c.c.). When the solubility of the pyrimidine allowed, cold solutions were used and crystallisation of the complex followed almost immediately. Solutions of the less soluble pyrimidines were mixed with the urea solution at the boil; the mixture was cooled quickly without shaking, and allowed to crystallise as far as possible at room temperature. The *complex* crystallised in a pure state and was collected, washed, and dried.

Complexes of Urea with Pyrimidines in a Ratio other than Equimolecular (*see Table* 2).—A complete solution of urea and the pyrimidine was obtained at the boil, a minimum of 10 c.c. of solvent being used per g. of urea. The filtered solution was cooled quickly, and the *complex* allowed to crystallise.

Complexes of 2-*Hydroxy*-4 : 6-*dimethylpyrimidine with Compounds related to Urea* (*see Table* 3).—The method followed was essentially that just described.

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357. *The Oxides of Uranium. Part III.* The System* UO_2–MgO–O.

By J. S. Anderson and K. D. B. Johnson.

A study of the binary system UO_2–MgO by means of a high-temperature vacuum furnace and *X*-ray diffraction measurements has revealed no evidence of compound formation at any temperature between 300° and 2350°, but solid solutions of magnesium oxide and uranium dioxide are formed. The solubility of magnesium oxide in uranium dioxide to give a fluorite structure with anion vacancies is only a few moles % even at the highest temperatures unless extra oxygen enters the solid-solution phase. This defect solid solution has a great affinity for oxygen, however, and when it is allowed to take up extra oxygen the solubility of magnesium oxide increases markedly, to as much as 25 moles %. Chemical analysis of these partially oxidised solid-solution phases shows that almost exactly one atom of oxygen is taken up for each molecule of magnesium oxide dissolved in uranium oxide to give a fluorite lattice having no vacant anion sites.

The magnesium oxide phase does not dissolve detectable quantities of uranium dioxide under any of the conditions studied.

The present work follows that of Part II * on the UO_2–CaO system, and is of some interest in that it involves one of the smallest bivalent cations and one of the largest quadrivalent cations. The Goldschmidt ionic radii are Mg^{2+}, 0·78 Å and U^{4+}, 1·05 Å (cf. Ca^{2+}, 1·06; Ti^{4+}, 0·64; Zr^{4+}, 0·89; Th^{4+}, 1·10). The disparity between the ionic radii of magnesium and uranium is greater than for the comparable double oxide systems previously described in the literature. Magnesium oxide and titanium dioxide form double oxides of the composition $2TiO_2$,MgO and TiO_2,MgO (v. Wartenberg and Prophet, *Z. anorg. Chem.*, 1932, **208**, 369), and magnesium oxide and zirconia are reported to form $MgZrO_3$ (*idem*, *ibid.*), although Ebert and Cohn (*ibid.*, 1933, **213**, 321) did not confirm this result. Magnesium oxide and thoria do not interact (v. Wartenberg and Prophet, *loc. cit.*) and neither oxide has a marked solubility in the other. We would therefore expect to find neither compound formation nor an extensive range of solid solutions between magnesium oxide and uranium dioxide. If found at all, solid solutions of magnesium oxide in thorium or uranium dioxides would be expected to have the cubic fluorite structure of the dioxides, with a contracted unit cell (UO_2, $a = 5{\cdot}457$ kx.u.; ThO_2, $a = 5{\cdot}5855$ kX.u.) due to the replacement of large ions by smaller ones, each dissolved magnesium oxide " molecule " being associated with an anion vacancy in the lattice.

The ThO_2–MgO system is free from any complications arising from variable valency of the components. On dimensional grounds it would be expected that the solubility of magnesia in thoria and in uranium dioxide should be similar. Whereas, however, the unit cell of thoria undergoes a shrinkage, corresponding to the dissolution of approximately 0·5 mole % of magnesium oxide, when thoria is heated to 2000° in vacuum with an excess of magnesium oxide, our results showed magnesia to have a much greater apparent solubility in uranium dioxide than would be expected on the basis of direct analogy. It became clear that the reason for the difference lay in the variable valency of uranium. This makes it possible for the solid-solution phase to take up sufficient oxygen to fill the lattice vacancies, the electrical neutrality of the crystal being maintained by a corresponding partial increase in charge of the uranium ions from U^{4+} to U^{5+}.† The experimental evidence presented supports the hypothesis that the solubility of magnesium oxide in " uranium dioxide " is, in fact, markedly increased by inclusion of sufficient additional oxygen to fill the anion sites which would otherwise have been vacant. The system corresponds rather

* Part II, *J.*, 1951, 1352.

† The same result could be achieved by formation of an appropriate proportion of sexavalent uranium ions, but there is evidence to show that in sexavalent uranium compounds the U^{6+} is invariably accompanied by two close O^{2-} ions, forming a structural unit unsuited for inclusion in the cubic fluorite structure of these solid solutions.

closely with the " controlled valency " semiconductors of Verwey and Haijman (*Philips Res. Report*, 1950, **5**, 173), who found, *e.g.*, that Li_2O and NiO would form solid solutions (NaCl type) only if Ni^{2+} could simultaneously be oxidised to Ni^{3+}. The resulting phase, $(Li_x\ Ni^{3+}{}_x Ni^{2+}{}_{1-2x})O$, is not anion-deficient.

At high temperatures, the extra oxygen taken up by the solid phase may be provided by dissociation of magnesium oxide, which begins at about 1700° in a vacuum of 10^{-5} mm. (Tiede and Birnbrauer, *Z. anorg. Chem.*, 1914, **87**, 129). For experiments above 1750°, the oxide mixtures used were prepared from the two separate oxides, but for much of the work below this temperature magnesium and uranous hydroxides were coprecipitated from aqueous solutions. The two oxides were thereby very intimately mixed, and the consequent reduction in the necessary diffusion path meant that equilibrium between these two refractory oxides could be attained in a reasonable period of heating at temperatures as low as 650°. In one case good *X*-ray photographs were obtained after heating the precipitated mixture at only 300° in a sealed tube in the presence of moisture. In coprecipitated preparations, heated at lower temperatures, oxygen is provided by the partial atmospheric oxidation which is unavoidable if uranous hydroxide is handled by the ordinary laboratory methods of wet chemistry.

Experimental

The sources of magnesium were the " AnalaR " oxide, which was heated in air to 1300° and stored in a desiccator before use, or the " AnalaR " sulphate. A very pure uranium dioxide was used for making powdered mixtures. " AnalaR " uranyl sulphate was reduced to uranous sulphate by irradiation with ultra-violet light in ethyl alcohol (see Hutchison and Elliott, *J. Chem. Phys.*, 1948, **16**, 920) to obtain the starting material for preparation of coprecipitated oxide mixtures. This uranous sulphate was washed with ethyl alcohol and dried. The magnesium and uranous hydroxides were coprecipitated rapidly in a finely-divided form, by running an aqueous solution of the two sulphates in a stream of fine droplets into mechanically stirred ammonia solution (*d* 0·88). The precipitate is initially green, but becomes black (through brown) during 30 min., owing to partial oxidation of the uranium. By working quickly, and drying the product in a nitrogen stream, this oxidation can be limited but not entirely prevented. These preparations were not normally reduced before use. Oxide mixtures of both types were pressed into pellets $\frac{1}{4}$" in diameter and $\frac{1}{2}$"—$\frac{3}{4}$" long just before they were needed

Furnace.—The high-temperature, high-vacuum furnace used was described by Alberman (*J. Sci. Instr.*, 1950, **27**, 280). The temperature was controlled by adjustment of the power input to the filament at a value determined by previous calibration against the m. p.s of pure nickel, platinum, and rhodium. The fourth-power radiation law was followed very accurately. The ambient pressure in the furnace during the final stages of heating was always close to 10^{-5} mm. Pellets heated to 1750° or less were contained in magnesia crucibles with lids. At the highest temperatures, however, magnesia crucibles disintegrated and in almost all cases the specimens prepared above 1750° were heated in small open tantalum crucibles which made contact with the pellet only at its base. When portions of the same oxide mixture were heated separately to 1950° in magnesia and in tantalum, the products were very slightly different owing, we believe, to the somewhat higher ambient oxygen pressure maintained inside the closed magnesia crucible. Traces of tantalum were detected in a few samples heated above 2000°, but in all cases the lower half of the pellet, at least, was rejected as being most susceptible to contamination by tantalum.

X-Ray Measurements.—Samples for *X*-ray diffraction measurements were normally taken from the top of the pellet, although an early experiment showed that there was no difference between such a sample and one from the powdered whole pellet. Finely ground material was loaded into Pyrex *X*-ray capillaries, and diffraction powder photographs were taken on 9-cm. Unicam cameras, filtered copper-$K\alpha$ radiation being used; $K\alpha_1$–α_2 doublets were usually resolved for all lines above $\theta = 60°$. Cell dimensions were calculated by Nelson and Riley's method (*Proc. Phys. Soc.*, 1945, **57**, 160) for graphical extrapolation to the value of a_{100} at $\theta = 90°$. Values quoted are accurate to $\pm 0{\cdot}001$ kX.U. unless otherwise stated.

Chemical Analysis.—The gross composition of the powdered preparations was fixed by weighing the pure oxides. The composition of the coprecipitated samples, however, was determined chemically, because precipitation of magnesium in ammonia solution (*d* 0·880) is

incomplete. The composition of the solid-solution phase in two-phase specimens containing free magnesium oxide can be determined by chemical analysis only after removal of free magnesium oxide. Magnesium oxide is soluble in 3M-ammonium chloride solution, while uranium dioxide and solid solutions rich in uranium dioxide are not, so that free magnesium oxide could be leached out from two-phase samples by gently boiling the powdered pellets in 3M-ammonium chloride solution. Leaching and chemical analysis of the solid-solution phase were performed in duplicate in all cases. This leaching was complete in the case of the comparatively well-crystallised samples made by heating the two oxides to high temperatures. The method was unsatisfactory for coprecipitated oxide mixtures which had been heated at temperatures below 1750°; it is presumably difficult to grind the sample down to particles comparable in size with the crystallites formed at these low temperatures, and inclusions of magnesium oxide remain. In the case of coprecipitated samples, therefore, the magnesium content had to be determined from the *X*-ray data, by use of the relationship between cell dimension and dissolved magnesium obtained for the well-crystallised samples, as described later.

For chemical analysis, the materials were dissolved in approximately 8M-nitric acid; 8M-ammonium nitrate solution was added and the uranium was extracted with ether. The method was that described by Rodden (*Analyt. Chem.*, 1949, **21**, 331), except that to obtain accurate results we found it essential to continue the extraction for 3 hr. instead of the 30 min. recommended. The uranium was determined gravimetrically as U_3O_8. The magnesium was determined as 8-hydroxyquinoline complex.

In some cases the solid-solution phase was analysed also for excess of oxygen (*i.e.*, that in excess of a composition represented by $x\mathrm{MgO},\mathrm{UO}_{2\cdot00}$), by reducing it for 2 hr. in hydrogen in a silica apparatus, and weighing the water produced. There is some difficulty in obtaining accurate analytical figures for magnesium and oxygen in these solid solutions, as both represent only a small molar fraction of a light element, contained in a small weight of uranium dioxide.

Controlled Oxidation Experiments.—In these, the oxygen uptake of a solid solution of magnesium oxide in uranium dioxide was measured quantitatively, in a Pyrex-glass high-vacuum system of the type commonly used for gaseous adsorption measurements. Pressure measurements in a calibrated volume were made by using a butyl phthalate manometer. The known quantity of gas was expanded into a second known volume containing the sample. The sample tube was mounted horizontally, and the powder shaken out in it to give a very thin layer, so that oxygen uptake would be uniform. It was heated by a small tube furnace, and small corrections were applied for the hot dead space. Samples were removed at intervals for *X*-ray measurements.

Results and Discussion

The principal features of the high-temperature experimental results are illustrated in the Table. In general, it was found that the *X*-ray photographs could be taken as indicating an equilibrium condition in the heated preparations only when they showed very sharp lines, with good resolution of doublets back to a Bragg angle of 60° or so. Quite good *X*-ray photographs were obtained from some of the specimens heated at 1100°, although further periods of heating showed that slow change occurred for as long as 30 hr. This was taken as evidence that the solid solution was of fairly uniform composition, and that the rate-controlling step in the attainment of equilibrium lies at the interface in this system. It must involve either the slow transfer of MgO or the slow attainment of an oxygen dissociation pressure equal to the ambient oxygen pressure surrounding the pellet in the vacuum. The latter seems the more likely for the following reason. The coprecipitated, partially oxidised MgO–UO_2 mixtures are initially amorphous, but if they are annealed in hydrogen at 650° for a short time (long enough to give a measurable *X*-ray photograph) they show that the original coprecipitated oxide is, in effect, a " supersaturated," though very poorly crystallised, solid solution which separates on heating. This separation occurs much more rapidly at 1000° in hydrogen than it does at 1100° in vacuum, suggesting that removal of oxygen is the rate-controlling factor.

It is convenient to consider the experiments in groups within which the same experimental technique was used throughout.

Preparations below 1750°.—These solid solutions were made by heating the coprecipitated oxides of gross composition 33 MgO : 67 UO_2. *X*-Ray diffraction measure-

ments on this series after being heated to temperatures between 1100° and 1750° (see Table) indicated that the solubility of magnesium oxide in uranium dioxide was large at 1100° and rapidly fell with rising temperature. This is, of course, contrary to the usual effect of temperature on the mutual solubility of solids. The results might at first sight be

Expt. No.	Initial composition, MgO : UO_2	Method of prepn.	Crucible.	Temp.	Heating time (hrs.)	*a*, kX.U.	Solid solution composition : Mg/U	excess O/U
33	33 : 67	Ppt.	MgO	1100°	1·0	5·293	—	—
34	,,	,,	,,	1325	1·0	5·332	—	—
35	,,	,,	,,	1525	1·0	5·390	—	—
36	,,	,,	,,	1750	1·0	5·419	—	—
43	,,	,,	,,	,,	2·0	5·422	0·078 *	0·041
37	,,	,,	,,	1100	2·0	5·292	—	—
38	,,	,,	,,	,,	6·0	5·309	—	—
40	,,	,,	,,	,,	12·0	5·311	—	—
41	,,	,,	,,	,,	30·0	5·319	0·306 *	0·323
44	,,	Ppt. reduced in H_2 at 1000°	,,	,,	2·0	5·406	0·114 *	0·084
26	40 : 60	Powder	Ta	1750	1·0	5·448	—	—
27	,,	,,	,,	,,	2·0	5·448	0·024	—
30	80 : 20	,,	,,	,,	2·0	5·4382	0·039	—
49	30 : 70	,,	,,	1000	1·0	5·448	—	—
51	50 : 50	,,	,,	,,	1·0	5·4424	—	—
54	10 : 90	,,	,,	2150	0·2	5·4502	—	—
50	30 : 70	,,	,,	,,	0·2	5·443	—	—
52	50 : 50	,,	,,	,,	0·2	5·4353	—	—
4	50 : 50	,,	,,	2350	0·1	5·427	—	—
14	50 : 50	,,	,,	1325	6·5	5·417	0·087	—
18	20 : 80	,,	,,	1515	2·0	5·445	0·031	—

* Determined from *X*-ray data.

explained by assuming a slow approach from the "supersaturated" condition of the coprecipitated oxides to a low equilibrium solubility. The rate of approach to equilibrium would be greater at higher temperatures. Long annealing at 1100° showed, however, that the cell dimension changed much more slowly than was observed in a reducing atmosphere at 1000°. It was known that the coprecipitated oxides had taken up some oxygen during preparation, and no attempt had been made to remove this extra oxygen by reduction, since it had been expected that the excess of oxygen would be lost in vacuum—slowly at 1100° and rapidly at higher temperatures, as is the case with β-UO_2 (which has a composition close to $UO_{2\cdot25}$; Alberman and Anderson, *J.*, 1949, S 303). Loss of oxygen on heating was indicated by an abnormally high ambient pressure in the vacuum furnace, and the completion of deoxygenation was inferred from the eventual fall in pressure to 10^{-5} mm. When a portion of the starting material was reduced in hydrogen, the loss in weight corresponded to an initial composition $(MgO)_{0\cdot5}(UO_{2\cdot369})$. When this reduced material was heated to 1100° in a vacuum, its cell dimension indicated a much smaller solubility of magnesium oxide than that of the unreduced material.

The solubility of magnesium oxide in uranium dioxide involves replacement of U^{4+} and $2O^{2-}$ by $Mg^{2+} + O^{2-} + \square O$ where $\square O$ represents a vacant oxygen site in the fluorite UO_2 lattice. It seemed possible that incorporation of sufficient oxygen to fill these vacant anion sites might appreciably increase the ability of the uranium dioxide phase to withstand the distortion involved by the inclusion of the much smaller Mg^{2+} ions, and might thus give rise to an increased magnesium oxide solubility. The solid solution phases were accordingly isolated by leaching them with ammonium chloride solution, and were analysed for magnesium, uranium, and excess of oxygen. The oxygen content was in fact, found to be less in solid solutions prepared at higher temperatures, and showed a smooth variation when compared with cell dimensions. Chemical analyses for magnesium on these poorly crystallised coprecipitated samples were not significant. The magnesium content in this series of preparations has therefore been determined from the *X*-ray diffraction values of the cell dimension, a_{100} (see Fig. 3). The justification for this method will appear later, when it will be shown that introduction of excess of oxygen alone, into a solid solution of fixed magnesium content, produces only a comparatively small change in unit-cell size.

There is a close parallel between magnesium oxide content, so determined, and excessive oxygen content, determined chemically, which is shown graphically in Fig. 1. The curve has a slope corresponding to the inclusion of just over one oxygen atom in excess per molecule of dissolved magnesium oxide. Equal proportions are required to maintain a solid solution in which the crystal lattice has no anion vacancies. It is noteworthy that when the anion vacancies are filled with extra oxygen, the solubility of MgO (involving the small Mg^{2+} ion) in UO_{2+x} at 1100° is greater than the solubility of CaO in $UO_{2\cdot0}$ at 1750° (in which case the cationic radii are almost identical, but the lattice is defective).

A marked solubility was observed after a moist precipitate of magnesium hydroxide and uranous hydroxide had been heated in a sealed Pyrex capillary for 2·5 hr. at 300°. A well-crystallised product was obtained, consisting of free U_3O_8, and a UO_2 phase with cell dimensions corresponding to $(MgO)_{0\cdot12}(UO_{2+x})$.

Preparations above 1750°.—A series of mixtures of various proportions of magnesium oxide and uranium dioxide, powdered together, were heated in tantalum to 1750°, 2000°, 2150°, and in one case to 2350° at which temperature the pellet softened. The apparent eutectic is therefore close to 2350°, though, strictly, a true eutectic temperature cannot

FIG. 1. *Relationship between magnesium content and excess oxygen content of solid-solution phases.*

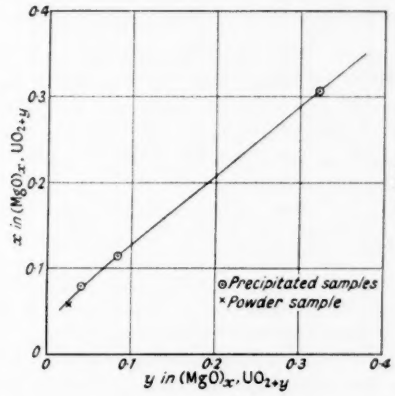
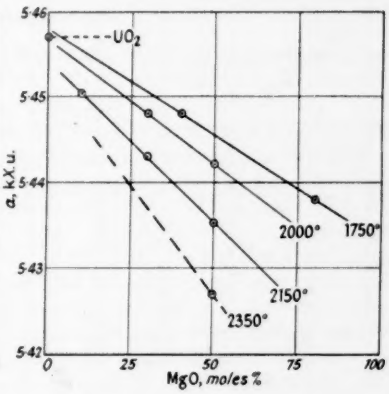


FIG. 2. *Change of* UO_2 *unit-cell dimension after heating mixtures of various gross compositions to* 1750°, 2000°, 2150°, *and* 2350°.



be obtained in vacuum, where the magnesium oxide is slowly dissociating and volatilising out of the hot zone.

For a normal two-component system, in which component A has a limited range of solubility in component B, a plot of gross composition against the cell dimensions of phase B (containing dissolved A) for a given temperature shows a continuous (usually linear) variation until saturation is reached; the cell dimension then remains constant in the two-phase region, where excess of A coexists with a saturated solution of A in B. The discontinuities in a family of such curves for a series of temperatures give a solubility curve. In this case, however, a constant cell dimension was not obtained in the two-phase region (see Fig. 2), implying that the solubility of magnesium oxide in uranium oxide depended upon the amount of excess of magnesium oxide in contact with the solid solution phase. Further heating showed that this effect was not merely an indication of an increased rate of solution but was a steady-state condition. The slope of the curves was not merely the initial part of the normal plot, since (*a*) chemical analysis showed the presence of ammonium chloride-soluble magnesium oxide, together with a solid-solution phase containing much less magnesium than would be necessary; (*b*) a family of curves was obtained, with different slopes; and (*c*) the *X*-ray diffraction lines of magnesium oxide appear on the photographs of mixtures richer in magnesium oxide than $30MgO : 70UO_2$.

Our interpretation of these results is based on the hypothesis that the oxygen pressure due to the dissociation of magnesium oxide occurring within the pellet was considerably above the ambient pressure maintained by the pumps and the "gettering" action of furnace parts. The resulting incorporation of oxygen led to a solubility of magnesium oxide in uranium dioxide which was favoured by higher temperatures and by the presence of more magnesium oxide. Direct chemical analysis for magnesium, uranium, and excess of oxygen, on one of the samples heated to 2150°, showed that the magnesium : excess of oxygen ratio lay on the curve obtained for the lower-temperature preparations (Fig. 1). The solubility of magnesium oxide in uranium dioxide at the highest temperatures is small, as compared with that observed between 1100° and 1525°.

The fact that the focal point of the family of curves lies so close to the cell dimension of uranium dioxide itself (Fig. 2) indicates that the solubility of magnesium oxide in it would be very small under all conditions if excess of oxygen were completely absent. This conclusion is supported also by the observations that (*a*) the solubility of magnesium oxide in thoria at 2000° as measured by us is only about 0·5 atom %; (*b*) the apparent eutectic temperature is 2350° for a 50 : 50 mixture, and higher still for a 30 : 70 mixture,

FIG. 3. *Variation of unit-cell dimension of solid-solution phase with dissolved* MgO *content.*

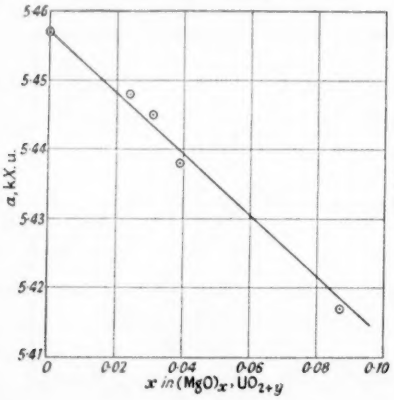
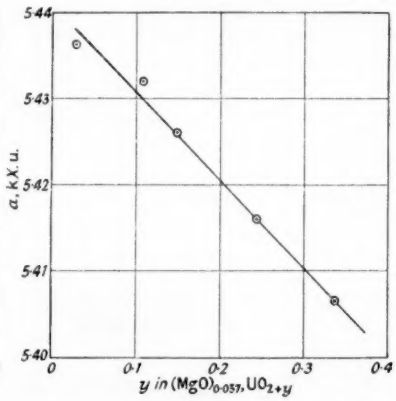


FIG. 4. *Variation of* UO_2 *unit-cell dimension with excess oxygen content, at fixed* MgO *content.*



values which are very close to the m. p. of the more fusible component magnesium oxide (2400°), and indicate very little mutual solubility; (*c*) the solubility of magnesium oxide in uranium dioxide, in a hydrogen atmosphere at 1000°, is very much less than the solubility of magnesium oxide in partially oxidised UO_2 at 1100°.

Oxidation of Solid Solutions.—As is normal in binary oxide systems, it was found throughout that there was a linear relationship between dissolved magnesium oxide concentration and cell dimension for specimens which could be directly analysed for magnesium (Fig. 3). This was very nearly true, irrespective of the treatment given before the high-temperature heating (*e.g.*, reduction in hydrogen or degassing temperature), over a temperature range from 1325° to 2150°. The determination of solubilities in solid systems from *X*-ray cell-dimension measurements is already an accepted technique, but in this case it was necessary to show that increasing the oxygen content by filling anion vacancies did not materially interfere with the method.

A controlled, stepwise oxidation was carried out at 400°, with a solid solution of the composition $(MgO)_{0·057}UO_{2·028}$, as determined chemically, in order to show the effect of varying the oxygen content in the presence of a fixed concentration of dissolved MgO. It was found that the size of the unit cell changed linearly without deviating from cubic symmetry as oxygen was added, up to a composition of $(MgO)_{0·057}$ $UO_{2·337}$, at which point the experiment was stopped. The values are presented graphically in Fig. 4. These results show that the change of cell dimension caused by introducing 1 mole % of magnesium

oxide into a uranium dioxide phase is approximately 5 times as great as the change caused by introduction of 1 atom % of excess of oxygen. This enables us to estimate the magnesium content of a solid solution phase from its cell dimension, although the accuracy would be reduced if very wide variation of oxygen content also occurred independently.

We are indebted to the Director, Atomic Energy Research Establishment, for permission to publish this work.

A.E.R.E., HARWELL, DIDCOT, BERKS. [*Received, January 22nd,* 1953.]

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358. *The Sommelet Reaction. Part IV.* The Preparation of Aliphatic Aldehydes.*

By S. J. ANGYAL, D. R. PENMAN, and G. P. WARWICK.

Aliphatic aldehydes are rapidly destroyed under the conditions of the Sommelet reaction, giving complex condensation products. Yet they can be obtained in yields of up to 50% by this reaction if they are removed by steam-distillation as they are formed. Trimethylacetaldehyde, which has no α-hydrogen atoms, is immune from the side reaction and can be made in 80% yield.

N-Alkylhexaminium halides are converted in good yield into dimethylalkylamines by hot formic acid and formaldehyde.

IT has been stated (Parts I and II, *J.*, 1949, 2700, 2704) that saturated aliphatic aldehydes are not obtainable by the Sommelet reaction. This is, indeed, true if the reaction is performed in the usual manner, *i.e.*, under reflux for one or more hours. Thus when *N*-hexylhexaminium bromide—or *n*-hexylamine hydrochloride, hexamine, and formaldehyde—was heated in water, 50% ethanol, or 50% acetic acid, no hexanal was obtained. Hexylamine, however, was not recovered; besides some neutral oil, the main product of the reaction, after acid hydrolysis, was a weakly basic oil which did not react with toluene-*p*-sulphonyl chloride and gave no crystalline salts. It boiled over a wide range up to 180°/1 mm.—the approximate molecular weight of the fractions ranging from 230 to 700—and a considerable residue was left. When any fraction was redistilled it again boiled over a wide range and left some residue; obviously condensation or polymerisation occurred during heating. Amongst the fractions the higher-boiling ones had a lower oxygen content, indicating that condensation occurred probably with the loss of water.

The failure to isolate an aldehyde does not prove that none was formed. It seemed unlikely that an aliphatic amine would have given rise to the complex condensation products; rather it appeared probable that an aldehyde was formed and then destroyed by side-reactions. To test this hypothesis, heptanal was submitted to the usual conditions of the Sommelet reaction: after 2 hour's heating only traces of it were recovered. Some polymeric aldehyde was present but the main product was a weakly basic oil, boiling over a wide range, similar to that obtained in the Sommelet reaction of hexylamine. However, it was found that condensation proceeded sufficiently slowly to allow the nearly quantitative recovery of the aldehyde if the reaction mixture was steam-distilled, instead of being heated under reflux.

Accordingly, the Sommelet reaction with hexamine was carried out in a current of steam and hexanal was indeed obtained in small yield; the weakly basic condensation products were again present. It was ascertained that some aldehyde was also produced by the reaction of hexylamine hydrochloride with formaldehyde, in the absence of hexamine (cf. Part I, *loc. cit.*). In this case, however, no polymeric condensation products were formed but hexylamine was recovered together with some methylhexylamine. It follows that ammonia as well as formaldehyde is required for the formation—probably by an initial reaction of the Mannich type—of the high-boiling products. Usually (Part I, *loc. cit.*) it is best to keep the ratio of hexamine to amine in the Sommelet reaction as high as practicable. In the preparation of aliphatic aldehydes, however, though hexamine is

* Part III, *J.*, 1950, 2141.

necessary, it promotes the side-reaction and therefore it is advisable to keep its proportion to the amine as *low* as possible. *E.g.*, when a solution of hexylamine hydrochloride was added dropwise to a solution of hexamine in 50% acetic acid, through which a current of steam passed, the yield of aldehyde was only 17%; but when a solution of *N*-hexylhexaminium bromide—or of hexylamine hydrochloride and hexamine—was added to 50% acetic acid in the same way the yield of aldehyde was 40—50%. The use of water or dilute ethanol as solvent resulted in somewhat lower yields.

By the same technique heptanal was prepared in 51% yield from *N*-heptylhexaminium iodide but the particularly reactive phenylacetaldehyde was obtained in 12% yield only.

A different technique was used for the isolation of the lower aldehydes. During the reaction, the mixture was distilled through a fractionating column at such a rate that the aldehyde passed over with the minimum amount of water. In this way *iso*valeraldehyde was obtained in 45% yield from *N-iso*amylhexaminium iodide; *n*-butaldehyde, however, probably owing to its greater reactivity, was isolated in only 16% yield. Methoxyacetaldehyde could not be obtained from 2-methoxyethylamine.

Since alkyl halides react slowly with hexamine it is necessary to perform this reaction in chloroform and to isolate the hexaminium salts before the actual Sommelet reaction. In order to produce the salts in yields over 80%, alkyl bromides and iodides require about 24 hr.' boiling, and the chlorides somewhat more. An attempt to increase the reaction rate by using a higher-boiling solvent such as chlorobenzene (Long and Troutman, *J. Amer. Chem. Soc.*, 1949, **71**, 2473) failed because of extensive decomposition of the quaternary salt.

The side reaction consuming the aldehyde was thought to involve the hydrogen atoms on the α-carbon atom; therefore an aldehyde with no α-hydrogen atoms, such as trimethylacetaldehyde, should be stable under the conditions of the Sommelet reaction and be obtainable by heating under reflux, as are aromatic aldehydes. This proved to be the case. Because of the well-known unreactivity of *neo*pentyl halides, no attempt was made to prepare a quaternary hexaminium compound but *neo*pentylamine was used as a starting material. The reaction was unusually slow, presumably for steric reasons: after 8 hr.' boiling in 50% acetic acid solution a 59% yield of trimethylacetaldehyde was obtained. There were no high-boiling condensation products: the basic material was nearly pure *neo*pentylamine. When the amount of recovered starting material was taken into account the yield of trimethylacetaldehyde was over 80%.

For identification a sample of dimethylhexylamine was required: but when it was prepared by the reaction of hexylhexaminium bromide with formic acid [a method successful with benzyl- and substituted benzyl-hexaminium salts (Sommelet and Guiot, *Compt. rend.*, 1922, **174**, 687; Part II, *loc. cit.*)] it was obtained in small yield only, accompanied by higher-boiling, weakly basic, condensation products. Yet the reaction of hexylamine, formaldehyde, and formic acid (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571) gave a satisfactory yield. It transpired that the formaldehyde present in combination in the hexaminium salt was insufficient to supply all the methyl groups required for complete methylation of both amine and ammonia: part of the amine therefore escaped methylation and underwent the Sommelet reaction and subsequent condensations. Addition of excess of formaldehyde resulted in a satisfactory yield of dimethylhexylamine.

Experimental

M.p.s are corrected. Microanalyses by Mrs. E. Bielski.

Preparation of Hexaminium Salts.—After a solution of the alkyl halide (0·2 mole) and hexamine (31 g.) in chloroform (200 ml.) had been boiled for 10 hr. the precipitated salt was filtered off, half of the solvent distilled off, and boiling continued for another 14 hr. during which more salt separated. Total yields were: from *n*-hexyl bromide, 78%; from *iso*amyl iodide, 82%; from *n*-heptyl iodide, 90%.

Hexanal.—(i) A solution of *n*-hexylamine hydrochloride (6·8 g.) in water (50 ml.) was added dropwise (15 min.) to a solution of hexamine (8·3 g.) in 50% acetic acid (50 ml.) through which steam was passed. Steam-distillation was continued until the distillate no longer gave a cloudiness with semicarbazide acetate. After the addition of concentrated hydrochloric acid

the distillate was extracted with ether which was shaken with sodium carbonate solution, dried, and distilled, giving 0·84 g. (17%) of hexanal, b. p. 128—130° (dinitrophenylhydrazone, m. p. 105·5—106·5°; lit., 107°).

The residue from the steam-distillation was evaporated several times with excess of hydrochloric acid and ethanol until all the formaldehyde was removed, and then made strongly alkaline. The liberated bases (5 g.) were extracted with ether and distilled at 1 mm., fractions being collected at 80—90°, 125—130°, and at 170—180°. Attempts to form solid derivatives were unsuccessful, nor could di- or tri-hexylamine be isolated from them. Fraction (i) (Found: C, 66·6; H, 11·6; N, 14·95%) had an average molecular weight of 230, as determined by " isothermic microdistillation " (Niederl, Kasanof, Kisch, and SubbaRao, *Microchemie*, 1949, **34**, 132); fraction (iii) (Found: C, 67·9; H, 11·5; N, 16·35%) had M = approx. 700.

(ii) When a solution of *n*-hexylamine hydrochloride (6·8 g.), hexamine (8·3 g.), and formaldehyde (3·7 ml. of 40%) in water (50 ml.) was added dropwise to 50% acetic acid (50 ml.) as above, 2·1 g. (42%) of aldehyde were obtained. When *N*-hexylhexaminium bromide was used, the yield was 49%.

(iii) *Without hexamine.* A mixture of *n*-hexylamine (6 g.), formaldehyde (4·5 ml. of 40%), and water (60 ml.) was boiled, after being adjusted to pH 5 with hydrochloric acid, under reflux for 1 hr. Excess of hydrochloric acid was added and the aldehyde separated in 6% yield by steam-distillation and ether-extraction. From the residue the basic material was isolated in the usual way; it boiled between 128° and 138° and was shown, by treatment with toluene-*p*-sulphonyl chloride, to consist mainly of *n*-hexylamine, with a small amount of a secondary amine.

Heptanal.—A suspension of *N*-heptylhexaminium iodide (40·7 g.) in water (150 ml.) was added in portions to 50% acetic acid (120 ml.) through which steam was passed. Worked up as above, 6·5 g. (51%) of heptanal, b. p. 152—154°, were obtained.

iso*Valeraldehyde.*—50% Acetic acid (300 ml.) was placed into a two-necked flask fitted with a fractionating column (Dufton) and a dropping funnel. After the solution was brought to the boil a suspension of *iso*amylhexaminium iodide (100 g.) in water was added during 30 min. The temperature at the column head was 90—95°; distillation was continued till it rose to 100°. The distillate (50 ml.), worked up as above, gave 11·5 g. (45%) of *iso*valeraldehyde, b. p. 91—93° (dinitrophenylhydrazone, m. p. 122°; lit., 123°).

Direct steam-distillation of the hexaminium salt dissolved in 50% acetic acid gave a 35% yield of the aldehyde.

Trimethylacetaldehyde.—*neo*Pentylamine was prepared by the sequence of reactions proposed by Hughes and Ingold (*J.*, 1933, 67). Treatment of pivalic acid with thionyl chloride, followed by concentrated ammonia solution, gave the amide in 73% yield. Distillation of the latter with phosphoric anhydride gave a 91% yield of the nitrile which was hydrogenated according to Walter and McElvain (*J. Amer. Chem. Soc.*, 1934, **56**, 1614). *neo*Pentylamine boils at 80—82°, its *toluene*-p-*sulphonyl* derivative is insoluble in dilute alkali solution and melts at 117° (Found: N, 6·0. $C_{12}H_{19}O_2SN$ requires N, 5·8%).

The amine (12·0 g.) was treated with concentrated hydrochloric acid to pH 5, then hexamine (21·6 g.), formaldehyde (10·4 ml. of 40%), acetic acid (14 ml.), and water (30 ml.) were added and the mixture boiled under reflux for 4 hr. After the addition of more hexamine (6 g.) and acetic acid (6 ml.) boiling was continued for 4 hr. Concentrated hydrochloric acid (30 ml.) was added and the mixture extracted with ether (3 × 25 ml.). The ethereal extract was washed with sodium carbonate solution, dried, and distilled through a short column: 7·0 g. (59%) of trimethylacetaldehyde, b. p. 77—78°, were obtained. The unchanged amine was recovered from the acidic reaction mixture by evaporation with concentrated hydrochloric acid and ethanol, and extraction of the residue with anhydrous ethanol. The hydrochloride thus obtained (5·5 g.) melted, after one crystallisation from ethanol–ether, at 273° (Hughes and Ingold, *loc. cit.*, m. p. 274°), the toluene-*p*-sulphonamide at 116°.

NN-*Dimethylhexylamine.*—(i) *N*-Hexylhexaminium bromide (21·6 g.) was heated on the water-bath with formic acid (25 ml.) and water (25 ml.) for 3 hr. The mixture was made alkaline and extracted with ether; distillation of the extract gave hexyldimethylamine, b. p. 146—150° (1·2 g., 13%), and a fraction boiling at about 275—280° (4·5 g.).

(ii) *N*-Hexylhexaminium bromide (20 g.), formic acid (51 ml.), and formaldehyde (50 ml. of 40%) were heated for 3 hr. on the water-bath. Five grams (60%) of hexyldimethylamine, b. p. 146—150°, were obtained.

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359. *The Sommelet Reaction. Part V.** N-*Heteroaromatic Aldehydes.*

By S. J. Angyal, G. B. Barlin, and P. C. Wailes.

In the pyridine and benzopyridine series α- and γ-aldehydes cannot be obtained by the Sommelet reaction but β-aldehydes are readily prepared. 4-Formyl-2-phenylthiazole, though an α-aldehyde, could be obtained in good yield.

The Sommelet reaction, best suited for yielding aromatic aldehydes, has not been used for the preparation of heteroaromatic aldehydes, except in the thiophen series (*e.g.*, Hartough, "Thiophene and Its Derivatives," Interscience Publ., New York, 1952, p. 310; Wiberg, *Org. Synth.*, 1949, **29**, 87). Since *N*-heteroaromatic aldehydes are generally difficult to obtain by other methods, it seemed worth while to explore the scope of the Sommelet reaction in their preparation.

The halogenomethyl compounds are not particularly suitable starting materials because in the *N*-heteroaromatic series they are mostly inaccessible or unstable. The aminomethyl compounds, on the other hand, are stable and available through the hydrogenation of nitriles.

2-Bromomethylquinoline, which is conveniently prepared (Hammick, *J.*, 1926, 1302), was first used but gave no aldehyde. Experience with aliphatic aldehydes (preceding paper) suggested that 2-formylquinoline may be unstable under the conditions of the Sommelet reaction, and this proved to be the case: short heating with a solution of hexamine destroyed it. 2-Formylpyridine and 3-formyl*iso*quinoline behaved similarly; the latter, expected to be more stable because of the lower bond order of the $N–C_{(3)}$ bond, was, in fact, converted into a black tar almost immediately by hexamine in boiling dilute acetic acid. It is clear therefore that α-aldehydes of pyridine and benzopyridines cannot be prepared by the Sommelet reaction.

4-Formylpyridine proved to be more stable: most of it was recovered after 10 min.', but none after 2 hr.', heating. Nevertheless experiments designed to remove it quickly by steam-distillation from a reaction mixture of 4-aminomethylpyridine and hexamine failed to yield any of the aldehyde.

By contrast, the β-aldehydes are stable and can be prepared by the Sommelet reaction; *e.g.*, 3-formylpyridine, not readily available by other methods, is obtained easily from 3-aminomethylpyridine. 4-Formyl*iso*quinoline was obtained in 50% yield from the corresponding aminomethyl compound.

In the thiazole series, 4-formyl-2-phenylthiazole—though an α-aldehyde—was readily prepared but the isomeric 2-formyl-4-phenylthiazole could not be obtained by this method. Yet the latter compound, when prepared by other methods (Olin and Johnson, *J. Amer. Chem. Soc.*, 1931, **53**, 1470), was stable under the Sommelet conditions. 4-Chloromethyl-2-methylthiazole was too unstable to be of use in the Sommelet reaction, not even the hexaminium salt being obtainable.

Attempts to prepare furfuraldehyde from 2-aminomethylfuran failed.

Experimental

M. p.s are corrected. Microanalyses are by Mrs. E. Bielski.

3-*Formylpyridine*.—A mixture of 3-aminomethylpyridine (11·4 g.) (Huber, *J. Amer. Chem. Soc.*, 1944, **66**, 876), hexamine (18 g.), concentrated hydrochloric acid (26 ml.), acetic acid (4 ml.), and water (24 ml.) was boiled under reflux for 6 hr. After having been adjusted to pH 5, the mixture was saturated with sodium nitrate and extracted several times with chloroform (200 ml. in all). The solvent was removed through a short column (the aldehyde is

* Part IV, preceding paper.

somewhat volatile with chloroform), and the residue distilled, to give 6·4 g. (57%) of the aldehyde, b. p. 95—97°/15 mm. The *dinitrophenylhydrazone*, crystallised from aqueous pyridine, had m. p. 259° (Found: N, 24·1. $C_{12}H_9O_4N_5$ requires N, 24·4%). The oxime melted at 150°; Craig and Hixon (*J. Amer. Chem. Soc.*, 1931, **53**, 4367) report m. p. 148°.

pH 5 was used for extraction as a compromise: at lower pH's very little aldehyde is extracted and at higher pH's much of it is present as Schiff's bases. These are not absent even at pH 5, as shown by the substantial residue left on distillation of the aldehyde; the actual yield of 3-formylpyridine is probably higher than stated.

4-*Aminomethylisoquinoline*.—4-Cyano*iso*quinoline (19·8 g.) was hydrogenated at room temperature and pressure with Raney nickel in anhydrous ethanol saturated with ammonia. The reaction stopped when 4·2 l. of hydrogen had been taken up; after removal of the catalyst and solvent the mixture was distilled and fractions of the following b. p. were collected: (i) 80—100°/3 mm. (2·6 g.), (ii) 140—160°/2 mm. (6·7 g.), (iii) 210—215°/2 mm. (5·5 g.). The first consisted mainly of *iso*quinoline, b. p. 224—226° (picrate, m. p. 223°; methiodide, m. p. 158°; both identified by mixed m. p.). In view of the unusual nature of this reaction it was ascertained that *iso*quinoline was not an impurity of the starting material. Fraction (ii) was neutralised to pH 6·5 with hydrochloric acid, evaporated, and crystallised from ethanol–ethyl acetate, giving *4-aminomethylisoquinoline hydrochloride* (5·0 g., 20%), m. p. 208—209°. For analysis it was sublimed at 165°/0·003 mm. and then melted at 209—210° (Found: C, 61·5; H, 5·6; N, 14·5. $C_{10}H_{11}N_2Cl$ requires C, 61·7; H, 5·7; N, 14·4%). The free amine boils at 179—181°/6 mm. and readily forms a dihydrochloride, insoluble in ethanol. The *picrate* melts at 215° (Found: N, 17·65. $C_{16}H_{13}O_7N_5$ requires N, 18·1%).

The unsatisfactory yield could not be improved by increasing the pressure of the hydrogenation. When both pressure and temperature were increased, none of the expected amine was obtained.

4-*Formylisoquinoline*.—A solution of 4-aminomethyl*iso*quinoline hydrochloride (1·57 g.) and hexamine (2 g.) in 50% acetic acid (10 ml.) was boiled under reflux for 2 hr. The mixture was then diluted with water and extracted with ether, the ether evaporated, and the residue crystallised from water, to give the *aldehyde* (0·63 g., 50%), m. p. 100°. Another crystallisation raised the m. p. to 103° (Found: N, 9·05. $C_{10}H_7ON$ requires N, 8·9%). The *semicarbazone*, m. p. 253°, crystallised from much ethanol (Found: N, 26·5. $C_{11}H_{10}ON_4$ requires N, 26·2%). The phenylhydrazone, m. p. 201°, crystallised from dilute acetic acid.

4-*Formyl*-2-*phenylthiazole*.—4-Chloromethyl-2-phenylthiazole (2·0 g.) (Hooper and Johnson, *J. Amer. Chem. Soc.*, 1934, **56**, 484) and hexamine (1·6 g.) in 50% acetic acid (10 ml.) were boiled for 45 min. On cooling and dilution with water an oil separated which was taken up by ether and converted into the bisulphite compound. This was decomposed by sodium carbonate solution, to give the *aldehyde* (1·0 g., 56%), m. p. 49°. Being very soluble in organic solvents it is not readily crystallised; for analysis it was twice sublimed *in vacuo* and then melted at 52° (Found: N, 7·3. $C_{10}H_7ONS$ requires N, 7·4%). The *semicarbazone* formed needles (from methanol or ethyl acetate), m. p. 198° (Found: C, 53·45; H, 4·2. $C_{11}H_{10}OSN_4$ requires C, 53·65; H, 4·1%). A sample of the aldehyde was oxidised by permanganate to 2-phenylthiazole-4-carboxylic acid, m. p. 175°; Huntress and Pfister (*J. Amer. Chem. Soc.*, 1943, **65**, 1669) report m. p. 175—176·5°.

2-Formyl-4-phenylthiazole was prepared according to Olin and Johnson's method (*loc. cit.*). Though it was described as an oil, it readily crystallised on steam-distillation, and had m. p. 62°. It gave a bisulphite compound.

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360. *The Sommelet Reaction. Part VI.* Methyleneamines. A Proposed Mechanism for the Reaction.*

By S. J. Angyal, D. R. Penman, and G. P. Warwick.

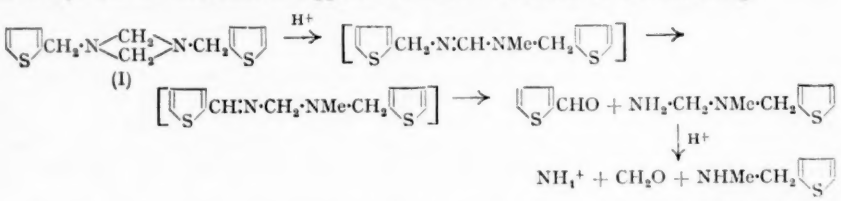
Molecular-weight determinations have shown that the methylene derivatives of benzylamine, *p*-nitrobenzylamine, and 2 : 4 : 6-trimethylbenzylamine are trimeric; they depolymerise during distillation. Since no evidence was found for the existence of a dimer, the mechanism postulated for the Sommelet reaction by Hartough and Dickert (*J. Amer. Chem. Soc.*, 1949, **71**, 3922) is without foundation. Methyleneamines are rapidly hydrolysed by acids even in the cold and therefore their salts, though they can be prepared in anhydrous solvents, have only transient existence in hot aqueous solution.

A probable mechanism for the Sommelet reaction is proposed and discussed.

Methyleneamines play an important part in the Sommelet reaction (Part I, *J.*, 1949, 2700). Since reports on their physical and chemical properties are in many respects conflicting, some of these properties have been studied further.

Our work was prompted particularly by recent papers of Hartough *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 4013, 4018) on *N*-methylenethienylmethylamines. Methylene-2-thienylmethylamine showed a peculiar behaviour on distillation: although it appeared to boil at about 100°/0·5 mm. it had to be heated to 170—180° before distillation took place; the distillate was liquid and, although it had no constant boiling point or refractive index, the authors assumed it to be the dimer and ascribed to it the structure (I). After redistillation, for which the same superheating was necessary, the liquid solidified to the crystalline trimer.

Hartough and Dickert (*ibid.*, 1949, **71**, 3922) observed that " hydrolysis " of the alleged dimer with dilute acid at pH 3 to 6·8 gave 2-formylthiophen and *N*-methyl-2-thienylmethylamine. This is the Sommelet reaction, which occurs with other methyleneamines in the same circumstances (Part I, *loc. cit.*; Graymore, *J.*, 1947, 1116). Hartough and Dickert rejected the mechanism suggested in Part I in favour of the following:



No evidence was presented for any of the steps in the above series of reactions, which were based solely on the assumption of structure (I) for the starting material and this assumption, in turn, was justified mainly by the production of 2-formylthiophen and methyl-2-thienylmethylamine, supposedly by the above series of reactions.

We have investigated the molecular weight, the behaviour on distillation, and the hydrolysis of methyleneamines. Our results do not accord with Hartough and Dickert's assumptions.

Molecular Weights.—Ingold and Piggott (*J.*, 1922, **121**, 2795) advanced the theory that azomethines dimerise to compounds containing a four-membered ring, methylene-*p*-toluidine being given as a stable example of this type (Ingold and Piggott, *J.*, 1923, 2745). The validity of their conclusions hinged on the molecular weight of methylene-*p*-toluidine for which the single value of 254 was reported (dimer, 238). However, by careful cryoscopic measurements in four solvents, Miller and Wagner (*J. Amer. Chem. Soc.*, 1932, **54**, 3698) have shown that the compound is trimeric at low temperatures (5—80°). In molten

* Part V, preceding paper.

camphor, however, the molecular weight was nearer to a dimer (213); and the vapour at 250°, as Ingold and Piggott (1923, *loc. cit.*) have shown, is monomeric.

This variation of the degree of polymerisation of methyleneamines with the temperature explains the conflicting reports: *e.g.*, Graymore (*J.*, 1947, 1116) stated that methylenebenzylamine and methylene-*p*-nitrobenzylamine were dimers (Rast method) but Mayer and English (*Annalen*, 1918, **417**, 76) found methylene-*o*-nitrobenzylamine to be trimeric (ebullioscopy in chloroform); Fuson and Denton (*J. Amer. Chem. Soc.*, 1941, **63**, 654) obtained a slightly higher than double molecular weight for a compound which was later shown (Part II, *J.*, 1949, 2704) to be methylene-2 : 4 : 6-trimethylbenzylamine (ebullioscopy in chloroform).

We determined the molecular weights at room temperature by the method of "isothermic microdistillation" (Barger, *J.*, 1904, **85**, 286; *Ber.*, 1904, **37**, 1754), using the improved procedure of Niederl, Kasanof, Kisch, and Subba Rao (*Microchemie*, 1949, **34**, 132). The crystalline methylene compounds of benzylamine, *p*-nitrobenzylamine, and 2 : 4 : 6-trimethylbenzylamine were found to be trimeric. Further, methylenebenzylamine does not dissociate in the concentration range 0·03—0·08M; the variations in molecular weight were within the experimental error. At room temperature therefore the crystalline stable methyleneamines are trimeric.

Distillation.—Irregular distillation is not peculiar to methylenethienylmethylamine. Methylenebenzylamine behaved in the same way: considerable overheating (oil-bath at 180—200°) was necessary, the vapours passing over at 100—130°/1 mm., showing no definite boiling temperature. Redistillation proceeded in the same way. The distillate was viscous and gradually solidified to a glass which crystallised during several days and was then found to be pure trimer. The crystalline trimer distilled over the same temperature range, overheating being necessary, and it did not solidify immediately in the receiver.

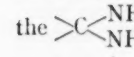
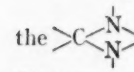
The boiling point is too high for a monomer (the isomeric benzylidenemethylamine boils at 90—91°/30 mm.; Ingold and Shoppee, *J.*, 1929, 1204), but too low for a dimer which would probably boil higher than dibenzylamine (186°/19 mm.). It is evident that the methyleneamine vaporises by depolymerisation for which a high temperature is required; hence the need for overheating. The observed vapour temperature is that of an overheated monomer. Condensation does not result in immediate trimerisation; the liquid may contain some monomer, but is probably a mixture of polymers which is gradually converted into the trimer, the most stable form. A similar process occurs in the preparation of methylenebenzylamine by mixing solutions of benzylamine and formaldehyde: an oil separates at once but does not crystallise immediately even on inoculation. The presence of hydroxyl ions appears to hasten the formation of crystalline trimer. On the other hand, when the pure trimer was dissolved in alcohol and precipitated by the addition of water, it immediately crystallised.

It was considered a possibility that Hartough's "dimer" contained some methylenebisamine, R·NH·CH_2·NH·R. An alleged compound of this type, methylenebisbenzylamine, was reported by Kampff (*Annalen*, 1890, **256**, 220) but it appears to have been the trimer of methylenebenzylamine (Hunt and Wagner, *J. Org. Chem.*, 1951, **16**, 1792). Methylenebisamines formed from aromatic amines, however, are well known (Eberhardt and Welter, *Ber.*, 1894, **27**, 1804; Bischoff and Reinfeld, *ibid.*, 1903, **36**, 41). The preparation of methylenebisbenzylamine was therefore attempted. When two mols. of benzylamine were treated with one mol. of aqueous formaldehyde a heavy oil separated after the addition of water. A few crystals of methylenebenzylamine gradually separated; when freed from benzylamine by water, the oil solidified and was identified as methylenebenzylamine. Distillation of this oil gave two fractions consisting of benzylamine and methylenebenzylamine, respectively. It appears therefore that the oil consists mainly of benzylamine and its methylene compound; whether methylenebisbenzylamine is present, probably in equilibrium with the other two compounds, is a matter for conjecture; but if it is, it certainly does not survive distillation.

Hartough, Meisel, Koft, and Schick (*J. Amer. Chem. Soc.*, 1948, **70**, 4013) claimed that methylenethienylmethylamine, as prepared from thienylmethylamine and formaldehyde,

is dimeric and that the trimer is only obtained on distillation. We found, however, that the oil formed on mixing solutions of the amine and formaldehyde solidified to the trimer after some stirring and cooling, even more readily than methylenebenzylamine.

Methylene-*p*-nitrobenzylamine was also distilled: overheating was again necessary and the distillate, a brown oil, crystallised rapidly to the trimer.

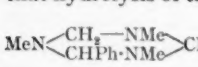
From these experiments it is concluded that there is no evidence for the existence of a dimer, and therefore Hartough and Dickert's reaction mechanism is without foundation. Even if such a dimer existed it is not likely that it would contain the four-membered ring of (I). The formation of methyleneamines being reversible, their structure will be determined by energy considerations. The trimer which is generally believed to contain a 1 : 3 : 5-triazine ring (cf. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill, New York, 1946, p. 513), is more stable than the monomer because the bond energy of six C–N bonds is apparently higher than that of three C:N bonds: Pauling ("The Nature of the Chemical Bond," Cornell Univ. Press, New York, 1940, pp. 53, 131) gives 48·6 kcals./mole for the C–N bond and 94 kcals./mole for C:N. A four-membered ring would have the same bond energies as a six-membered one; but it would have considerably more energy owing to strain and therefore would be less stable. Indeed, although Hale and Lange (*J. Amer. Chem. Soc.*, 1919, **41**, 380) appear to have established the existence of the  system in derivatives of urea, it is doubtful if compounds containing the  ring have ever been prepared. [The example given in "The Ring Index" (Patterson and Capell, Reinhold Publ. Corp., New York, 1940, p. 34) is a compound of doubtful structure.]

There is another objecton against Hartough and Dickert's proposed course of the Sommelet reaction. As a second step, it includes the prototropic rearrangement of an azomethine system, which has been shown to occur only in a very strongly basic medium (Ingold and Shoppee, *loc. cit.*) and is "in the highest degree unlikely" (Shoppee, *Nature*, 1948, **162**, 619) under the slightly acidic conditions of the reaction.

In further support of their mechanism Hartough and Dickert refer to the yield of aldehyde obtained. Their mechanism allows only a 50% yield and Hartough and Dickert never obtained more. By coincidence, the method given in *Org. Synth.*, 1949, **29**, 87, also results in approximately a 50% yield from 2-chloromethylthiophen. In the presence of hexamine, however, the course of the reaction suggested by Angyal and Rassack (Part I, *loc. cit.*) allows higher yields; and it has been found that by improving the procedure, particularly by using 50% acetic acid solution (Part III, *J.*, 1950, 2141), a 74% yield of 2-formylthiophen is obtained either from 2-chloromethylthiophen or from 2-thienylmethylamine.

Final proof that aldehyde formation is not dependent on the presence of a dimer was afforded by showing that 2-formylthiophen could be obtained from the crystalline trimer of methylenethienylmethylamine. Hartough and Dickert's method for "hydrolysing the dimer" gave a comparable yield.

Distillation of methylenebenzylamine was tried after addition of a small amount of sulphuric acid. This might facilitate depolymerisation, in analogy with the aldehyde trimers. Distillation occurred as before but the distillate was quite fluid and did not crystallise. Acid hydrolysis yielded some benzaldehyde. This behaviour was reminiscent of Graymore and Davies's distillation (*J.*, 1945, 293) of *N*-benzylhexaminium chloride which yielded an oil, b. p. 70—72°/30 mm., to which they assigned structure (II). It was claimed that hydrolysis of their product yielded benzaldehyde, methylamine, and formaldehyde, the latter having been identified by smell alone. The boiling point is much too low, however, for a compound of structure (II). On repeating Graymore's experiment we found that the main fraction consisted of a mixture of benzylidenemethylamine and a smaller amount of benzyldimethylamine; no formaldehyde was found amongst the hydrolysis products. Thus when a hexaminium compound, or a methyleneamine, is heated with

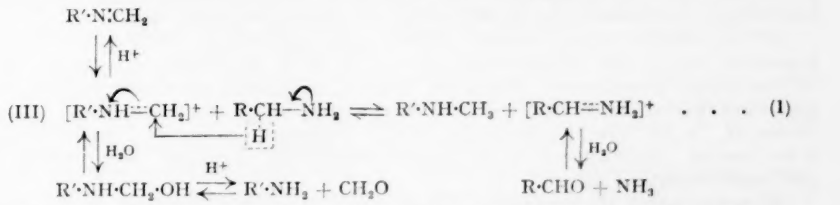

(II)

a strong acid in the absence of solvents, a Sommelet reaction occurs; the two cases are analogous, for in each a cyclic methyleneamine with one nitrogen atom in the quaternary state is involved.

Hydrolysis.—Hartough and Dickert (*loc. cit.*) claim that at pH 1—2 methylenethienylmethylamine exists as a salt of the monomer [evidence, stated to be in a paper by Hartough and Meisel (*J. Amer. Chem. Soc.*, 1948, **70**, 4019) is, however, not discernible]. Although methyleneamines, like most Schiff's bases, are rapidly hydrolysed by acids, they might form stable salts with strong aqueous acids. Under anhydrous conditions such salts were obtained, *e.g.*, methylenebenzylamine in anhydrous ether gave a monohydrochloride of the trimer, and a monopicrate of the trimer separated from anhydrous ethanol. After this work was completed, a hydriodide of the trimer was reported by Hunt and Wagner (*loc. cit.*). However, when the solvents contained small amounts of water, the salts, which were immediately precipitated, were the hydrochloride and picrate, respectively, of benzylamine. Methylenethienylmethylamine gave analogous results. In aqueous solutions, therefore, salts of the methyleneamines can have only transient existence [cf. the analogous results of Hunt and Wagner (*loc. cit.*) with alkylidenebisamines]. The water-insoluble methylenethienylmethylamine trimer dissolved immediately in an equivalent amount of N/10-hydrochloric acid, but the pH of the solution gradually increased from an initial value of *ca.* 2·2 to 3·7. This indicates that the compound dissolves first as the salt of a weak base (the Schiff's base) but then changes to the salt of a stronger base (thienylmethylamine); the half-life of the conjugate acid, in 0·04M-solution at 15°, is approximately 1 min.

Mechanism of the Sommelet Reaction.—In Part I (*loc. cit.*) it was shown that the Sommelet reaction is essentially a hydrogenation–dehydrogenation process in which a Schiff's base is hydrogenated at the expense of an amine. Several related reductions of Schiff's bases are known, such as the Plöchl–Eschweiler, the Leuckart, and the Wallach reaction, which have been extensively studied by Wagner and his school. (For leading references see McLaughlin and Wagner, *J. Amer. Chem. Soc.*, 1944, **66**, 251; Staple and Wagner, *J. Org. Chem.*, 1949, **14**, 559.) The reaction discussed by McLaughlin and Wagner (*loc. cit.*) is particularly similar to the Sommelet reaction. All these reactions appear to be acid-catalysed.

It is believed that the active intermediate is the conjugate acid of a Schiff's base, the mesomeric cation $R\cdot{}^{+}NH{:}CH_2 \longleftrightarrow R\cdot NH\cdot CH_2^{+}$ (III). This contains a strongly electrophilic carbon atom which can attack water (hydrolysis of the Schiff's base), aromatic rings (aminomethylation), activated methylene groups (Mannich reaction; Liebermann and Wagner, *J. Org. Chem.*, 1949, **14**, 1001), formaldehyde (Plöchl–Eschweiler reaction), or formic acid (Wallach and Leuckart reactions). In the last two cases a hydrogen atom with its two bonding electrons, *i.e.*, a hydride ion, is transferred to the cation, as in certain other organic redox reactions (Alexander, "Principles of Ionic Organic Reactions," Chapman and Hall, London, 1950, pp. 167—170). It is suggested that the mesomeric cation may similarly attack amines, abstracting a hydride ion according to the following proposed mechanism for the Sommelet reaction (horizontal sequence of the scheme):

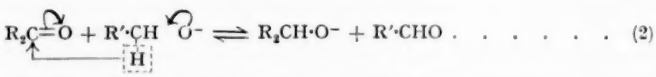


In the most favourable form of the reaction, *i.e.*, when hexamine is used, R' = H.

In aqueous solution the main reaction of the mesomeric cation will be hydrolysis according to the vertical sequence of the scheme. This process is much faster than the Sommelet reaction, hence in strongly acid solution it goes to completion without discernible formation of aldehyde. Only in the pH range in which the amine and the methylene-

amine are in equilibrium—and (III) is constantly re-formed—can the slower Sommelet reaction gain preponderance. The proposed mechanism therefore explains the pH limits (*ca.* 3—7) of the Sommelet reaction : amine and Schiff's base must coexist for the reaction to occur.

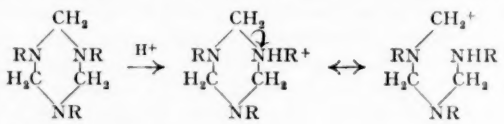
It may be noted that amines are ammono-alcohols, and Schiff's bases ammono-carbonyl compounds; therefore reaction (1) is the ammono-analogue of the reaction between carbonyl compounds and alcoholic alkali (Alexander, *op. cit.*) :



(2)

In the aquo-system (2), owing to the strong electron-affinity of the oxygen atom, the carbonyl carbon atom is sufficiently electrophilic to attract the hydride ion; but the alcohol will not release it until its electron density has been increased by its transformation into an alkoxide ion (Hammett, " Physical Organic Chemistry," McGraw-Hill, 1940, p. 361). On the other hand, in the ammono-system (1) the amine releases the hydride ion (amines, when un-ionised, are readily oxidised) but the Schiff's base is not sufficiently electron-attracting until converted into its conjugate acid. Hence the different pH requirements of these two reactions.

The cation (III) can be formed not only from Schiff's bases but also from hydroxymethylamines or from methylenebisamines (Staple and Wagner, *loc. cit.*). A similar cation can result as a first step in the acid hydrolysis of trimeric methyleneamines :



and in an analogous way also from hexamine.

While the proposed mechanism cannot be regarded as proved, it is compatible with all the known features of the Sommelet reaction. The electronic effects of groups attached to the carbon and nitrogen atoms account for the direction of the reaction and for some of its limitations. Two aspects of the present work seem to support this mechanism : (i) the demonstration that the conjugate acid of methyleneamines has a definite, though short, existence in aqueous solution : (ii) the fact that a Sommelet reaction occurs when the conjugate acids of Schiff's bases are heated in the absence of a solvent.

Experimental

M. p.s are corrected. Microanalyses by Mrs. E. Bielski.

Materials.—Methylenebenzylamine was prepared from a solution of benzylamine hydrochloride by the addition of excess of formaldehyde and excess of sodium hydroxide solutions. An oil separated which became semi-solid. Crystallisation from aqueous ethanol at −10° gave a 95% yield of colourless crystals, m. p. 50°. Methylenethienylmethylamine, m. p. 55°, was prepared in the same way in 90% yield, and crystallised from ethanol.

p-Nitrobenzylamine hydrochloride (7·56 g.) was dissolved in ethanol (40 c.c. of 80%), and hexamine (5·6 g.) and formaldehyde (0·4 c.c. of 40%) were added. A cream-coloured precipitate formed immediately; after 5 min.' boiling, the solution was cooled, and the precipitated methylene derivative recrystallised from ethyl acetate (nearly colourless needles, m. p. 161·5°; Graymore, *loc. cit.*, 1947, reported m. p. 158°). Prolonged heating, as described by Graymore, is not needed. Methylene-2 : 4 : 6-trimethylbenzylamine, m. p. 150°, was prepared by Fuson and Denton's method (*loc. cit.*).

Molecular-weight Determinations.—These were carried out according to the directions of Niederl *et al.* (*loc. cit.*), with azobenzene as a standard and acetone as solvent. It was necessary to keep the capillaries in a room of approx. constant temperature. Found : for methylene-*p*-nitrobenzylamine, 490 (trimer requires 492); for methylene-2 : 4 : 6-trimethylbenzylamine 440, 458 (trimer requires 483).

The usual procedure was reversed in the case of methylenebenzylamine. Instead of com-

paring a solution of the compound with several concentrations of azobenzene, the azobenzene concentration was kept constant and three dilutions (0·03, 0·05, 0·08M) of the Schiff's base were used. If dissociation of the trimer occurred in dilute solution, the movements of the menisci plotted against the concentrations would lie on a curve and not on a straight line. A straight line, however, was obtained from which the molecular weight was calculated as 350 (trimer requires 357).

Salts of Methylenebenzylamine.—Dry hydrogen chloride was passed into a solution of methylenebenzylamine (0·5 g.) in anhydrous ether (100 c.c.). The precipitate which separated immediately was washed repeatedly with anhydrous ether and dried over sulphuric acid. The *hydrochloride* melted at 125° (Found: Cl, 9·75. $C_{24}H_{27}N_3$,HCl requires Cl, 9·0%). Methylenebenzylamine showed evidence of its ability to combine with more than one mol. of acid: the precipitate, before washing, contains Cl approx. 15%, and slowly decomposes with the liberation of hydrogen chloride and some benzaldehyde. Thorough washing, however, removes the excess of acid and the salt is then stable in dry air. The same experiment, but with ether saturated with water, resulted in a somewhat slower separation of leaflets which melted, alone and in admixture with benzylamine hydrochloride, at 248°.

A solution of methylenebenzylamine (0·5 g.) in anhydrous ethanol (10 c.c.) was added to a saturated solution (10 c.c.) of picric acid in anhydrous ethanol. The mixture was heated to the b. p.; on cooling, the *picrate*, m. p. 110° (0·38 g.), of the trimer crystallised (Found: N, 14·2. $C_{24}H_{27}N_3,C_6H_3O_7N_3$ requires N, 14·3%). Recrystallisation from aqueous alcohol gave benzylamine picrate, m. p. 196°. The same experiment, but with 95% ethanol, gave benzylamine picrate (1·0 g.), m. p. alone and in admixture with an authentic sample, 198°.

Salts of Methylenethienylmethylamine.—Dry hydrogen chloride was passed through a solution of methylenethienylmethylamine (0·5 g.) in anhydrous ether (100 c.c.). After thorough washing with anhydrous ether and drying over sulphuric acid, the *hydrochloride* of the trimer was obtained as colourless crystals, m. p. 118°, stable in dry air (Found: Cl, 9·3. $C_{18}H_{21}N_3S_3$,HCl requires Cl, 8·65%).

Apparently the Schiff's base of thienylmethylamine is somewhat less readily hydrolysed than that of benzylamine, because use of ether saturated with water gave a mixture of the hydrochlorides of thienylmethylamine and methylenethienylmethylamine. Recrystallisation from ethanol–ether gave leaflets, which melted, alone and in admixture with thienylmethylamine hydrochloride, at 188°. Hartough and Meisel (*loc. cit.*) report 188—189°.

Methylenethienylmethylamine (0·5 g.) in anhydrous ethanol (10 c.c.) gave, as above, the *picrate* (0·32 g.) of the trimer, which, recrystallised from anhydrous ethanol, melted at 133° (Found: N, 13·75. $C_{18}H_{21}N_3S_3,C_6H_3O_7N_3$ requires N, 13·9%). Recrystallisation from aqueous ethanol gave thienylmethylamine picrate, m. p. 175° (Hartough and Meisel, *loc. cit.*, report 181—182°). Only the latter was obtained from 95% alcohol.

2-Formylthiophen.—A mixture of 2-chloromethylthiophen (41·5 g.), hexamine (88 g.), and 50% acetic acid (260 ml.) was heated under reflux for 4 hr. Concentrated hydrochloric acid (125 ml.) was added and heating continued for 5 min. After cooling, the mixture was extracted with ether (3 × 100 ml.), and the extract dried and evaporated. Distillation of the residue gave a fore-run of acetic acid and then the aldehyde (26 g., 74%), b. p. 63—66°/6 mm.

Distillation of N-Benzylhexaminium Chloride.—The salt (70 g.) was heated *in vacuo* to 200°, whereupon it decomposed and a colourless oil (14·2 g.) distilled at 68—86°/24 mm. On redistillation the main fraction boiled at 86—91°/30 mm. Three grams were hydrolysed by steam-distillation with excess of hydrochloric acid; benzaldehyde was determined in the distillate as its 2:4-dinitrophenylhydrazone, m. p. 237°: 2·08 g. of aldehyde were found. A test for formaldehyde with resorcinol and concentrated sulphuric acid was negative.

The residue from the steam-distillation was evaporated to dryness and the resulting solid extracted with chloroform. The insoluble material (0·89 g.) was methylamine hydrochloride, m. p. 223°. The chloroform-soluble hydrochloride (0·33 g.) gave a base, b. p. 165—172° (picrate, m. p. 94·5°, undepressed by benzyldimethylamine picrate).

Hydrolysis of Methylenethienylmethylamine.—A solution of methylenethienylmethylamine (125 mg.) in ethanol (5 ml.) was quickly added to 0·05N-hydrochloric acid (20 ml.). The pH of the solution was measured at frequent intervals with a Leeds and Northrup Universal pH Potentiometer Assembly. The following are minutes and pH's: ¼, 2·4; ½, 2·55; 1, 2·85; 1½, 3·0; 2, 3·15; 3, 3·3; 4, 3·45; 5, 3·52; 10, 3·65; 15, 3·7.

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361. *Perfluoroalkyl Grignard Reagents. Part II.* Reaction of Heptafluoropropylmagnesium Iodide with Carbonyl Compounds, and the Mechanism of Reduction during Grignard Reactions.†*

By R. N. Haszeldine.

The interaction of heptafluoropropylmagnesium iodide and acet-, prop-, and butyr-aldehyde, yields the expected secondary alcohols; with the corresponding perfluoro-aldehydes the secondary perfluoro-alcohol is obtained, but reduction to primary alcohol and formation of a polymer of fluoro-aldehyde also occurs. Acid chlorides yield fluoro-ketones and tertiary alcohols; esters give tertiary alcohols, fluoro-ketones and, by reduction, the secondary 1-(perfluoropropyl)alkanols. Reaction of heptafluoropropylmagnesium iodide with esters of perfluoro-acids forms a convenient preparation of perfluoro-ketones, reduction of which with lithium aluminium hydride also affords the secondary perfluoro-alcohols.

The current theory of Grignard reactions is supported by the addition and reduction products obtained by interaction of methyl-, ethyl-, and propylmagnesium iodide and fluoro-aldehydes, -ketones, and -esters, but must be modified to explain the reduction occurring in reactions of perfluoroalkyl Grignard reagents. The influence of solvent, temperature, mode of addition, and magnesium bromide on the yields of addition and reduction products in reactions of certain Grignard reagents has been investigated.

The reaction of heptafluoropropylmagnesium iodide with a variety of carbonyl compounds has thrown light on the mechanism of reduction of the latter by Grignard reagents.

Acetaldehyde, propaldehyde, and butyraldehyde react smoothly but slowly with heptafluoropropylmagnesium iodide in butyl ether at −50° to give severally 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol (I; R = Me), 4 : 4 : 5 : 5 : 6 : 6 : 6-heptafluorohexan-3-ol (I; R = Et), and 5 : 5 : 6 : 6 : 7 : 7 : 7-heptafluoroheptan-4-ol (I; R = Pr), in 40—45% yields.

$C_3F_7 \cdot CHR \cdot OH$ (I) $\quad RCH_2 \cdot OH$ (II) $\quad C_3F_7 \cdot COR$ (III) $\quad (C_3F_7)_2CR \cdot OH$ (IV)

If the formation of Grignard compounds is initiated with a small portion of the fluoroiodide, and a mixture of heptafluoroiodopropane and the aldehyde is added at low temperature, the yields of the alcohol (as I) are appreciably reduced (25—30%). Alternate addition of heptafluoroiodopropane and only 40% of the quantity of aldehyde theoretically required to react with the Grignard reagent thereby formed (*i.e.* at least 1 equiv. of Grignard reagent in excess throughout) gives yields (40—45%) comparable with those obtained in the first experiments. The products of the Grignard reaction therefore do not interfere with the formation of the heptafluoropropylmagnesium iodide, and the low yields in the second series of experiments are caused by the absence of an excess of Grignard reagent throughout the reaction (see later).

Substantially more heptafluoropropane and fluorine-free material of higher boiling point were produced under the conditions of the second series of experiments, and a possible explanation is that aldol-type condensations are brought about by the Grignard solution. This is also indicated in the reaction of heptafluoropropylmagnesium iodide and acetone (Part I *), since further examination of the residue has revealed the presence of mesityl oxide and phorone (*ca.* 8%).

Perfluoro-acetaldehyde, -propaldehyde, and -butyraldehyde give somewhat lower yields (30%) of the secondary alcohols (I) than their unsubstituted analogues, and the reaction is much slower. Best yields were achieved at −10° to −20° (see Table 5), although the thermal decomposition of the heptafluoropropylmagnesium iodide was thereby increased. The fluoro-aldehydes cannot undergo the aldol condensation, since they

* Part I, *J.*, 1952, 3423.

† Taken from papers presented at A.C.S. Meetings, New York, 1951; Atlantic City, 1952

contain no α-hydrogen atoms, and most of the fluoro-aldehyde not giving the secondary alcohol was recovered as aldehyde polymer or as free aldehyde (15—40%), or was reduced to the corresponding primary alcohol (II; R = CF_3, C_2F_5, or C_3F_7) (5—10%). The mechanism of reduction is discussed in more detail below. The polymerisation of the fluoro-aldehydes to a white solid, from which the monomer can be regenerated by heat, can be observed at low temperature in the reaction mixture; similar polymerisation does not take place in reactions with alkyl Grignard reagents (see below).

The fluoro-alcohols (I; R = CF_3, C_2F_5, and C_3F_7) are the first secondary-perfluoro-alcohols prepared, and their ionisation constants, with those of other fluoro-alcohols, are discussed in the following paper.

Acid chlorides do not usually give good yields of ketone when treated with an alkyl-magnesium halide, since addition of a second molecule of Grignard reagent to the intermediate ketone is often fast. When acetyl, propionyl, or butyryl chloride reacts with heptafluoropropylmagnesium iodide, however, the fluoro-ketone formed as intermediate reacts with excess of Grignard reagent more slowly than does an unsubstituted ketone, so that the ketones (III; Me, Et, and Pr) are isolated in 15—20% yield and the *tert.*-alcohols (IV; R = Me, Et, and Pr) are obtained in *ca.* 25% yield. The formation of the *sec.*-alcohol (I; R = Me, Et, or Pr) was not detected (cf. fluoro-esters, below). The corresponding fluoro-acid chlorides give moderately good yields (30—40%) of the perfluoro-ketones (III; R = CF_3, C_2F_5, and C_3F_7), with lower yields of the *tert.*-alcohols (*ca.* 15%), again illustrating the decreased reactivity of the carbonyl groups in the perfluoro-ketones relative to the alkylfluoroalkyl and dialkyl ketones.

It is noteworthy that ethyl heptafluorobutyrate was a by-product (3%) when ether was used as solvent, presumably formed by cleavage of the ether catalysed by magnesium halides:

$$C_3F_7{\cdot}COCl + Et_2O \xrightarrow{MgX_2} C_3H_7{\cdot}CO_2Et + EtCl$$

(cf. Underwood and Wakeman, *J. Amer. Chem. Soc.*, 1930, **52**, 387; Kyrides, *ibid.*, 1933, **55**, 1209; Descudé, *Compt. rend.*, 1901, **132**, 1129).

The reaction of an ester with a Grignard reagent is commonly used for the preparation of *tert.*-alcohols, but with heptafluoropropylmagnesium iodide appreciable yields of ketones (particularly perfluoro-ketones) can also be obtained. Ethyl acetate, propionate, and butyrate react smoothly with the Grignard reagent at −50° to give three main products, the fluoro-ketones (III; R = Me, Et, and Pr), the *sec.*-alcohols (I; R = Me, Et, and Pr) arising by reduction of the ketone (see later), and the *tert.*-alcohols (IV; R = Me, Et, and Pr). When the ester is added to the Grignard reagent the yields are *ca.* 10%, 10%, and 20—30%, respectively, *i.e.*, the overall yield is low. Use of equimolar amounts of ester and Grignard reagent gives higher yields of ketone and lower yields of the *tert.*-alcohol than when a ratio *ca.* 1 : 2 is employed; the function of the excess of Grignard reagent is discussed below. Ethyl trifluoroacetate and ethyl pentafluoropropionate give considerably higher yields (40%) of the perfluoro-ketones (III; R = CF_3 or C_2F_5) and about equal yields of (I and IV; R = CF_3 and C_2F_5).

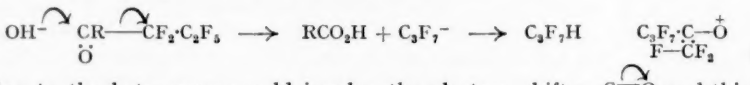
Addition of the Grignard reagent to the unsubstituted ester gives greatly increased yields (40%) of the ketone, no change in the amount of secondary alcohol formed, and a slight reduction in the amount of *tert.*-alcohol obtained. Similar addition to the fluoro-esters gives tertiary (5%) and secondary (5%) alcohols and an increased yield of ketone (50%). The absence of excess of Grignard reagent clearly facilitates ketone formation. The interaction of fluoro-esters and the fluoroalkyl Grignard reagent provides a simple route for the preparation of fluoro-ketones.

The addition of ethereal magnesium bromide solution to the ester before addition of the latter to heptafluoropropylmagnesium iodide does not affect the amount of ketone formed, but there is a marked decrease in the reduction to the secondary alcohol (discussed below) and a slight increase in yield of *tert.*-alcohol.

The fraction of higher boiling point from the above reactions in ether is believed to contain the hemiketal $C_3F_7{\cdot}CR(OEt){\cdot}OH$, since, on decomposition during distillation, small amounts of the perfluoro-ketone and ethyl alcohol were liberated, but precise charac-

terisation could not be effected. Fluoro-ketones and -aldehydes are known to form stable dihydrates, and chloral forms a dihydrate and a hemiacetal.

The various fluoro-ketones obtained show the marked decrease in boiling point on replacement of hydrogen by fluorine, attributed to decreased hydrogen bonding, *viz.*, C_3H_7·COMe, 102°; C_3H_7·COEt, 124°; C_3H_7·COPr, 144°; C_3F_7·COMe, 58°; C_3F_7·COEt, 78°; C_3F_7·COPr, 100°; C_3F_7·$COCF_3$, 29·5° (22°); $C_3F_7COC_2F_5$, 52° (56°); C_3F_7·COC_3F_7, 75° (82°). A similar effect is observed with the *sec.*-fluoro-alcohols (following paper). The boiling points of fluorocarbons containing the same number of carbon atoms, given above in parentheses, show that replacement of two fluorine atoms by an oxygen atom causes only slight change. The decreased basicity of the carbonyl oxygen atom on a fluoro-ketone relative to its hydrocarbon analogue is shown by the insolubility of (III; R = C_2F_5, and C_3F_7) in sulphuric acid and the low solubility in water, although hydrate formation as found with hexafluoroacetone is still apparent. The ketones (III; R = Me, Et, Pr, and C_3F_7) are readily cleaved by dilute sodium hydroxide to give heptafluoropropane, and the reaction of the heptafluoropropyl compound is notably more rapid, despite the decreased water solubility. It is suggested that the haloform reaction involves displacement at the keto-group rather than addition to it:



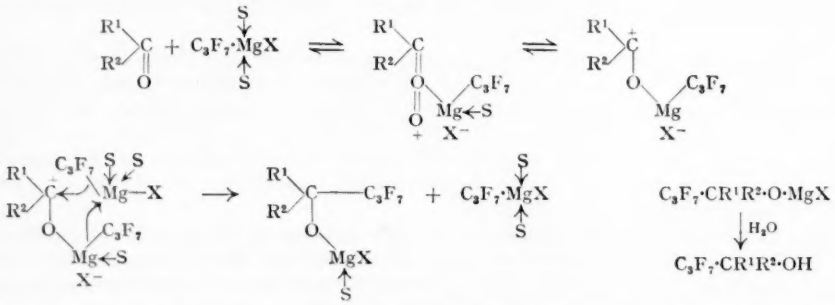
(*A*)

Addition to the keto-group would involve the electron shift $>C{=}\overset{\frown}{O}$ and this would be opposed by the inductive effect of the fluoroalkyl group and, probably at least as important in the case of fluorine, by hyperconjugation effects (see *J.*, 1952, 3490), *e.g.* (*A*). It is noteworthy that the reaction of heptafluoropropylmagnesium iodide with the fluoro-ketones is markedly slower than with the unsubstituted ketones.

Lithium aluminium hydride reduction of the ketones prepared above gives an alternative and convenient method for the preparation of the *sec.*-alcohols (I; R = Me, Et, Pr, CF_3, C_2F_5, and C_3F_7). Conversely, oxidation of (I; R = Me, Et, and Pr) by Conant and Quayle's general technique (*Org. Synth.*, Coll. Vol. I, p. 211) gives the ketones in good yield. The *tert.*-alcohols mentioned above will be described in detail in a later paper.

The reactions of heptafluoropropylmagnesium iodide will now be examined in the light of current theories of Grignard reaction.

Complex Formation and Effect of Solvent and Concentration of Reactants.—It is assumed (see Swain and Boyles, *J. Amer. Chem. Soc.*, 1951, **73**, 870; Mosher and Combe, *ibid.*, 1950, **72**, 3994, for references) that the reaction of the solvated Grignard reagent (S = ether of solvation) with, say, a ketone or aldehyde, involves formation by co-ordination of a 1 : 1-complex which, in the second step of the reaction, is attacked by a *second* molecule of the Grignard reagent, with transfer of a $C_3F_7^-$ ion in a six-membered ring complex. Hydrolysis then yields the alcohol:



The reactions of heptafluoropropylmagnesium iodide adequately support this scheme. For example, if an excess of the Grignard reagent is not present during most of the reaction, formation of the 1 : 1-complex can occur, but the subsequent step involving a second

molecule of the Grignard reagent can proceed only slowly; this is illustrated by the decreased yields of the *sec.*-alcohols when acetaldehyde, propaldehyde, and butyraldehyde react with heptafluoropropylmagnesium iodide in a molar ratio >1 : 2. A 3 : 1 molar ratio of the Grignard reagent to ester is similarly advantageous in the preparation of *tert.*-alcohols.

The effect of changing R^1 and/or R^2 from alkyl to perfluoroalkyl cannot be predicted with certainty by the above scheme, since opposing factors are involved. Thus, if R^1 and R^2 are perfluoroalkyl, the reduced basicity of the carbonyl oxygen atom will not favour co-ordination of magnesium to oxygen, which is an electrophilic attack; on the other hand, the nucleophilic attack of the perfluoropropyl ion on the carbonyl carbon atom will be favoured. Again, the ionic nature of the carbon–magnesium bond in heptafluoropropylmagnesium iodide (see Part I) will make the magnesium compound a stronger acid (in the Lewis sense) than, say, propylmagnesium iodide, so that the electrophilic attack and subsequent polarisation of the carbonyl double bond should be facilitated; opposing this will be the fact that displacement of ether of solvation (S) from the strongly solvated Grignard reagent will be difficult. The net effect of the factors is that the ease of reaction of heptafluoropropylmagnesium iodide with a ketone COR^1R^2 decreases in the order R^1, R^2 = alkyl > R^1 = alkyl, R^2 = perfluoroalkyl > R^1, R^2 = perfluoroalkyl.

Reduction during the Reactions of Alkyl Grignard Reagents.—Swarts (*Bull. Soc. chim. Belg.*, 1927, **36**, 191), Campbell, Knobloch, and Campbell (*J. Amer. Chem. Soc.*, 1950, **72**, 4380), and recently McBee, Higgins, and Pierce (*ibid.*, 1952, **74**, 1387, 1736) have shown that fluorine-containing carbonyl compounds react with methylmagnesium iodide only by addition, but that with other alkyl Grignard reagents both reduction and addition occur. The experiments between methyl-, ethyl-, and propyl-magnesium iodides and ethyl heptafluorobutyrate, trifluoroacetaldehyde, heptafluorobutyraldehyde, and heptafluorobutyl methyl ketone, summarised in Table 1, confirm and extend these results.

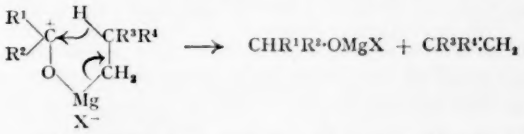
TABLE 1.

Compound	Grignard reagent	Redn. product, %	Addn. product, %	Ketone, %	Compound	Grignard reagent	Redn. product, %	Addn. product, %
$C_3F_7{\cdot}CO_2Et$	MeMgI [1]	0	70	—	$C_3F_7{\cdot}CHO$	PrMgI [1,5]	72	8
	EtMgI [1,2]	62	15	—		PrMgI [6]	46	26
	MeMgI [3]	0	51	5		PrMgI [7]	39	33
	EtMgI [3]	45	8	10				
					$C_3F_7{\cdot}COMe$	MeMgI [1]	0	71
$CF_3{\cdot}CHO$ ...	MeMgI [1]	trace	65	—		EtMgI [1]	59	14
	PrMgI [1,4]	77	5	—		MeMgI [8]	0	66
						EtMgI [8]	22	37

[1] Compound added to Grignard reagent. [2] Ethylene liberated. [3] Grignard reagent added to compound. [4] Propylene liberated (58%). [5] Propylene liberated (42%). [6] Aldehyde plus magnesium bromide added to Grignard reagent. [7] Grignard reagent added to aldehyde plus magnesium bromide. [8] Ketone plus magnesium bromide added to Grignard reagent.

It should be noted that the percentage reduction during the reactions of fluorine-containing carbonyl compounds is higher than with the corresponding unsubstituted compounds.

Whitmore's explanation (Whitmore, Atlantic City Meeting, Amer. Chem. Soc., April 1943; see also Swain and Boyles, *loc. cit.*) of the reduction observed during reactions of Grignard reagents is given considerable support by the results in Table 1. Reduction can occur if the formation of a complex from the alkyl Grignard reagent $CHR^3R^4{\cdot}CH_2{\cdot}MgX$ and the carbonyl compound is followed by internal rearrangement with hydride ion shift.



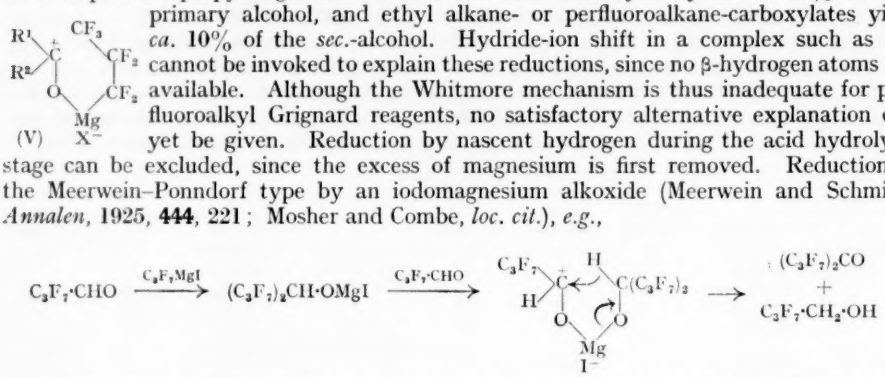
$\longrightarrow$ $CHR^1R^2{\cdot}OMgX + CR^3R^4{:}CH_2$

Methylmagnesium iodide gives high yields of only the addition product, since there are no β-hydrogen atoms available for transfer as hydride ion, whereas ethyl- and propyl-

magnesium iodides react mainly by reduction. The second molecule of the alkyl Grignard reagent acts only as a source of hydride ion, and its efficiency as a reducing agent will depend not only on the number of β-hydrogen atoms available, but also on the ease of transfer of hydride ion from the alkyl groups. This transfer will be facilitated if R^3 or R^4 is an electron-releasing group, and particularly if it can undergo hyperconjugation with the incipient double bond of the olefin $CR^3R^4{:}CH_2$ in the transition state. There is thus a marked similarity between the influence of the alkyl groups in the alkylmagnesium halide and the alkyl groups in alkyl halides undergoing nucleophilic or elimination reactions.

The fluoro-aldehydes (Table 1) and chloral (Gilman and Abbot, *J. Org. Chem.*, 1943, **8**, 234) are reduced to the primary alcohol only during reactions involving Grignard reagents which contain β-hydrogen atoms. Further support for Whitmore's mechanism is given by the marked increase in the ratio of addition to reduction product when magnesium bromide is added to the fluoro-aldehyde or -ketone before its reaction with the alkyl Grignard reagent (Table 1); this is ascribed to the greater efficiency of magnesium bromide relative to the alkylmagnesium halide in co-ordinating to the carbonyl oxygen, thus preventing formation of the complex and, by polarising the carbonyl double bond, facilitating the addition reaction.

Reduction during Reactions involving Perfluoroalkyl Grignard Reagents.—On treatment with heptafluoropropylmagnesium iodide, the fluoro-aldehydes yield 5—10% of the primary alcohol, and ethyl alkane- or perfluoroalkane-carboxylates yield *ca.* 10% of the *sec.*-alcohol. Hydride-ion shift in a complex such as (V) cannot be invoked to explain these reductions, since no β-hydrogen atoms are available. Although the Whitmore mechanism is thus inadequate for perfluoroalkyl Grignard reagents, no satisfactory alternative explanation can yet be given. Reduction by nascent hydrogen during the acid hydrolysis stage can be excluded, since the excess of magnesium is first removed. Reduction of the Meerwein–Ponndorf type by an iodomagnesium alkoxide (Meerwein and Schmidt, *Annalen*, 1925, **444**, 221; Mosher and Combe, *loc. cit.*), *e.g.*,



is plausible, but must also be excluded, since such a compound can be formed only during ester reactions; furthermore, the aldehyde or ketone, which should also be formed, was not detected. There is no evidence for or against a free-radical mechanism for the reduction, *e.g.*,

$$COR^1R^2 + \cdot MgI \longrightarrow \dot{C}R^1R^2{\cdot}OMgI \xrightarrow[H_2O]{RH} CHR^1R^2{\cdot}OH + R\cdot$$

apart from the low temperatures used, which would not favour radical formation.

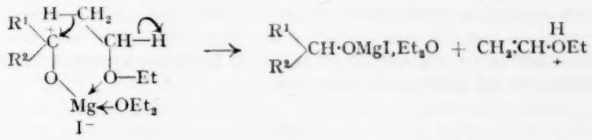
In the reactions of ethyl heptafluorobutyrate with methyl-, ethyl- or propyl-magnesium iodide, and of heptafluoropropylmagnesium iodide with ethyl acetate, propionate, or butyrate, the same intermediate, $C_3F_7{\cdot}CR(OMgI){\cdot}OEt$ (R = Me, Et, or Pr) is formed, but although the same reduction product, $C_3F_7{\cdot}CHR{\cdot}OH$, is produced, the yields are vastly different, as shown in Table 2.

TABLE 2. *Yield of secondary alcohol, %.*

MeMgI + $C_3F_7{\cdot}CO_2Et$	0	$C_3F_7{\cdot}MgI$ + $MeCO_2Et$	8
EtMgI + „	62	„ + $EtCO_2Et$	9
PrMgI + „ (predicted)	>50	„ + $PrCO_2Et$	14

Reduction must occur after the formation of $C_3F_7{\cdot}COR$, therefore, and must involve a second molecule of the Grignard reagent. This is supported by the fact that magnesium bromide, added to an ester before its reaction with heptafluoropropylmagnesium iodide, is preferentially co-ordinated to the $C_3F_7{\cdot}COR$ intermediate and thereby prevents its reduction by the heptafluoropropylmagnesium iodide.

Since the reduction involves the solvated molecule of the Grignard compound, a possible mechanism involves hydride-ion shift from the ether of solvation:



Such a mechanism could be tested by preparation of heptafluoropropylmagnesium iodide in a solvent containing no, or only unreactive, hydrogen atoms, so that hydride-ion transfer from the solvent of solvation would be impossible, but the successful preparation of the Grignard reagent in perfluorotriethylamine, diperfluorobutyl ether, or benzene has so far proved unsuccessful.

Experimental

General Technique.—Sealed Pyrex-glass tubes (50—500 ml.) were used for small-scale experiments, and conventional Grignard apparatus for larger-scale experiments. Extreme precautions were taken to exclude oxygen, carbon dioxide, and moisture. Heptafluoroiodopropane (*J.*, 1949, 2856; 1952, 4259) was dried, purified, and stored *in vacuo*. Spectroscopically pure magnesium was treated as described in Part I (*loc. cit.*). Ethyl and *n*-butyl ethers were used as solvents, the former where possible, the latter where it facilitated isolation of the product. Part I showed that more basic solvents (*e.g.*, tetrahydropyran, tertiary amines) give better yields of the Grignard reagent, but for general convenience the ethers are preferred. Grignard formation was initiated by addition at 0° to −20° of *ca.* 5% of the total fluoro-iodide, and the temperature was then lowered as rapidly as possible without stopping formation of the Grignard reagent. The remaining fluoro-iodide was then added, and the yield of Grignard reagent taken from the data of Part I, periodic checks being made by parallel experiments involving carboxylation or hydrolysis. Yields of reaction products are based on the quantity of heptafluoropropylmagnesium iodide available for reaction, and if low yields were obtained the products of two or three experiments were combined.

The volatile by-products, hexafluoropropene and heptafluoropropane (see Part I), were usually removed before the excess of magnesium was filtered off.

Traces of water were removed from the fluoroalkyl alcohols by heating them at 50° with phosphoric anhydride before final distillation. The perfluoroalkyl alcohols were distilled from phosphoric anhydride without decomposition. The fluoro-ketones form hydrates, boiling in the 90—100° region, which were decomposed at 50—60° by phosphoric anhydride before final distillation.

The fluoroalkyl Grignard reagents invariably yield by-products, often unidentified and of high boiling point. In view of the difficulties of separation of the products, the yields reported are only minimum.

Reaction of Heptafluoropropylmagnesium Iodide with Acetaldehyde, Propaldehyde, and Butyraldehyde.—The aldehydes were carefully purified, dried, and stored in a vacuum system. Heptafluoropropylmagnesium iodide (65% yield) was prepared from heptafluoroiodopropane (10·0 g.) and magnesium (3·2 g.) at −50° in *n*-butyl ether (150 ml.) during 12 hr., and into it was passed an excess of the appropriate aldehyde (3·0 g., 3·2 g., 4·0 g., severally) during 5 hr. The mixture was stirred for 36 hr., and then allowed to warm to room temperature during 24 hr., before being heated at 60° for 1 hr. and filtered. Hydrolysis with ammonium chloride solution, separation, and drying (P_2O_5) and distillation of the ethereal layer gave 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol (41%), b. p. 101° (see Part I), 4 : 4 : 5 : 5 : 6 : 6 : 6-*heptafluorohexan*-3-*ol* (45%), b. p. 114—115° (Found: C, 31·8; H, 3·2%. $C_6H_7OF_7$ requires C, 31·6; H, 3·1%), and 5 : 5 : 6 : 6 : 7 : 7 : 7-*heptafluoroheptan*-4-*ol* (40%), b. p. 128—130°, 71°/60 mm. (Found: C, 34·6; H, 3·5%. $C_7H_9OF_7$ requires C, 34·7; H, 3·7%). The use of ethyl ether as solvent for the reaction with propaldehyde and butyraldehyde, with otherwise identical conditions, gave the corresponding alcohols in 49 and 46% yields. Unchanged aldehyde was isolated in every experiment.

In a separate series of experiments, heptafluoroiodopropane (3·0 g.) was slowly added to magnesium (3·2 g.) in *n*-butyl ether (120 ml.) at −25°, and the mixture cooled to −50°. Immediate addition of a cooled solution of heptafluoroiodopropane (7·0 g.) and the aldehyde

(3·0 g., 3·2 g., 3·9 g., severally) in *n*-butyl ether (30 ml.) was begun and completed during 3 hr. The respective alcohols were obtained in yields of 31, 26, and 24%.

The yields, %, of heptafluoropropane, hexafluoropropene, and recovered heptafluoroiodopropane (based on heptafluoropropylmagnesium iodide), and of the unidentified fluorine-free material (yield based on the aldehyde) which distilled at 155—210° and was distinct from the fluoropolymer described in Part I, are given in Table 3 for the separate (S) and concurrent (C) addition of the aldehyde to the reaction mixture.

TABLE 3.

	C_3F_7H		C_3F_6		C_3F_7I		Higher-boiling material	
	(S)	(C)	(S)	(C)	(S)	(C)	(S)	(C)
MeCHO	15	23	3	2	11	17	12	26
EtCHO	10	22	1	1	9	15	12	31
PrCHO	7	19	—	—	8	13	10	27

The hexafluoropropene and heptafluoropropane were separated as described in Part I.

When addition of 0·5 ml. portions of heptafluoroiodopropane in *n*-butyl ether during Grignard formation was alternated with addition of 40% of the aldehyde theoretically required to react with the Grignard reagent thereby formed, the yields of the fluoro-alcohols were 42, 43, and 42%, respectively.

Reaction of Heptafluoropropylmagnesium Iodide with Trifluoroacetaldehyde, Pentafluoropropaldehyde, and Heptafluorobutyraldehyde.—The aldehydes, prepared by reduction of the corresponding fluoro-acids with lithium aluminium hydride, were stored in a vacuum system at −183° to prevent polymerisation, and were added to the Grignard solution as gases. An attempt to use the solid polymer of trifluoroacetaldehyde was unsuccessful. Heptafluoropropylmagnesium iodide was prepared in 60—65% yield at −50° in *n*-butyl ether from magnesium (3·2 g.) and heptafluoroiodopropane (10·0 g.) during 12—18 hr. The fluoro-aldehyde (3·0 g., 3·8 g., 5·1 g., severally) was then added during 8 hr., the mixture allowed to warm (4 hr.) to room temperature, and stirring continued for 24 hr. 1 : 1 : 1 : 3 : 3 : 4 : 4 : 5 : 5 : 5-*Decafluoropentan*-2-*ol* (29%), b. p. 51—52°/209 mm. (Found: C, 22·3; H, 0·7; F, 70·7. $C_5H_2OF_{10}$ requires C, 22·4; H, 0·7; F, 70·9%), 1 : 1 : 1 : 2 : 2 : 4 : 4 : 5 : 5 : 6 : 6 : 6-*dodecafluorohexan*-3-*ol* (30%), b. p. 61°/150 mm. (Found: C, 22·6; H, 0·6. $C_6H_2OF_{12}$ requires C, 22·6; H, 0·6%), and 1 : 1 : 1 : 2 : 2 : 3 : 3 : 5 : 5 : 6 : 6 : 7 : 7 : 7-*tetradecafluoroheptan*-4-*ol* (27%), b. p. 70°/103 mm. (Found: C, 22·6; H, 0·6. $C_7H_2OF_{14}$ requires C, 22·8; H, 0·5%), were obtained.

The variation in yield, %, of the secondary alcohols with temperature is shown in Table 4. In these experiments the Grignard reagent was prepared at −50° and warmed rapidly to the temperature shown before addition of the aldehyde. The other reaction products were heptafluoropropane, hexafluoropropene, the fluoro-aldehyde (isolated as the polymer and as the hydrate in approximately equal amounts), and the primary alcohols corresponding to the aldehydes, *i.e.*, trifluoroethanol, pentafluoropropanol, and heptafluorobutanol (Haszeldine and Leedham, *loc. cit.*; Haszeldine, *J.*, 1950, 2789) and freed from traces of aldehyde hydrate by distillation from phosphoric anhydride.

TABLE 4.

	C_3F_7·CHX·OH			XCH_2·OH			XCHO, recovered		
X =	CF_3	C_2F_5	C_3F_7	CF_3	C_2F_5	C_3F_7	CF_3	C_2F_5	C_3F_7
−50°	29(32)	30(29)	27(30)	4(5)	3(—)	4(2)	31(18)	—	40
−30	33	31	38	—	—	—	34	—	—
−20	38	42(46)	43(46)	5	6(3)	8(5)	24	15	18
−10	40	39	41	4	—	—	—	—	—

The results of parallel experiments with ethyl ether as solvent are recorded in parentheses in Table 4.

The formation of the fluoro-aldehyde polymer, observed at −50°, tended to slow the reaction by coating effects, but with prolonged stirring the normal amount of magnesium dissolved, as estimated by weighing the magnesium obtained by filtration before hydrolysis.

Reaction of Acid Chlorides with Heptafluoropropylmagnesium Iodide.—The acid chlorides were prepared from the corresponding acids and phosphorus pentachloride and were purified *in vacuo*. Preliminary experiments showed that reaction with the Grignard reagent was slow below −40°, and that although the yields were approximately the same, the addition of pentafluoropropionyl or heptafluorobutyryl chloride to the Grignard reagent caused a faster reaction

than when the acyl halides were added during Grignard formation. In the following experiments heptafluoropropylmagnesium iodide was prepared at −50° and then warmed to −20°, and the acyl halide added during 3 hr. After being stirred for 24 hr., allowed to attain room temperature (12—15 hr.), and then heated to 50° for 30 min., the products were isolated in the usual way.

Acetyl chloride (2·0 g.) gave **3 : 3 : 4 : 4 : 5 : 5 : 5 :-*heptafluoropentan*-2-*one*** (15%), b. p. 58—59° (Found: C, 28·3%; *M*, 212. $C_5H_3OF_7$ requires C, 28·3%; *M*, 212), and the *tert.*-alcohol (22%) whose properties, with those of the *tert.*-alcohols mentioned below, will be discussed in a later paper. Propionyl chloride (2·1 g.) similarly gave **4 : 4 : 5 : 5 : 6 : 6 : 6-*heptafluorohexan*-3-*one*** (18%), b. p. 78° (Found: C, 31·8%; *M*, 225. $C_6H_5OF_7$ requires C, 31·9%; *M*, 226) and the *tert.*-alcohol (27%). Butyryl chloride (2·7 g.) yielded **5 : 5 : 6 : 6 : 7 : 7 : 7-*heptafluoroheptan*-4-*one*** (21%), b. p. 100° (Found: C, 35·3%; *M*, 240. $C_7H_7OF_7$ requires C, 35·0%; *M*, 240), and the *tert.*-alcohol (23%).

Trifluoroacetyl chloride (3·0 g.) was sealed with the Grignard reagent, and yielded the *tert.*-alcohol (11%) and ***perfluoropentan*-2-*one*** (36%), b. p. 29·5° (Found: C, 22·6%; *M*, 265. C_5OF_{10} requires C, 22·6%; *M*, 266). Pentafluoropropionyl chloride (3·6 g.) similarly gave the *tert.*-alcohol (13%) and ***perfluorohexan*-3-*one*** (41%), b. p. 52° (Found: C, 22·6%; *M*, 316. C_6OF_{12} requires C, 22·8%; *M*, 316). Heptafluorobutyryl chloride (4·8 g.), added in the conventional Grignard apparatus, gave the *tert.*-alcohol (16%) and ***perfluoroheptan*-4-*one*** (31%), b. p. 75° (Found: C, 23·1%; *M*, 364. C_7OF_{14} requires C, 23·0%; *M*, 366).

With ethyl ether as solvent, the following yields of ketones were obtained: C_3F_7·COEt 25%, C_3F_7·COPr 27%, C_3F_7·CO·C_2F_5 (not separated completely from solvent by distillation) 12%.

When the amount of acid chloride used was reduced by 50%, but with otherwise identical conditions and *n*-butyl ether as solvent, the following yields were obtained: C_3F_7·COMe 10%, C_3F_7·COEt 12%, C_3F_7·COPr 13%, C_3F_7·CO·CF_3 32%, C_3F_7·CO·C_2F_5 34%, C_3F_7·CO·C_3F_7 29%.

Reaction of Esters with Heptafluoropropylmagnesium Iodide.—(a) *Addition of ester to Grignard reagent.* The Grignard reagent was prepared at −50° as described above and, after addition of the ester (1 hr.), the reaction mixture was stirred at −40° for 24 hr., for a further 24 hr. during which it warmed to room temperature and finally for a further 24 hr. The volatile products were then removed and the filtered solution was hydrolysed with sulphuric acid. Table 5(*a*) gives the % yields of secondary alcohol, ketone, and tertiary alcohol obtained by reaction of the ester and Grignard reagent (amount present: 60—65% of theory from fluoroiodide used) in molar ratios of (i) 1 : 1 and (ii) 1 : 2·5.

TABLE 5(*a*).

Ester	Quantity, g.	C_3F_7·CHR·OH		RCO·C_3F_7		$(C_3F_7)_2$CR·OH	
		(i)	(ii)	(i)	(ii)	(i)	(i)
$MeCO_2Et$	1·8	2	8	19	11	21	32
$EtCO_2Et$	2·1	8	9	16	10	19	28
$PrCO_2Et$	2·5	15	14	13	5	12	18
CF_3·CO_2Et	2·9	—	8	—	41	—	8
C_2F_5·CO_2Et	4·0	—	6	—	39	—	10

TABLE 5(*b*).

$MeCO_2Et$	0·9	—	12	—	43	—	8
$EtCO_2Et$	1·1	—	7	—	37	—	7
$PrCO_2Et$	1·3	—	10	—	39	—	5
CF_3·CO_2Et	1·4	—	2	—	53	—	5
C_2F_5·CO_2Et	2·0	—	4	—	51	—	3

TABLE 5(*c*)

$EtCO_2Et$		—	0	—	8	—	26
$PrCO_2Et$		—	6	—	—	—	28
C_2F_5·CO_2Et		—	0	—	42	—	18

(b) *Addition of Grignard reagent to the ester.* Heptafluoropropylmagnesium iodide was added in five 20% aliquots to a solution of the ester in *n*-butyl ether at −50°, and the mixture then treated as in (*a*) above. The results are given in Table 5(*b*).

(c) *Addition of magnesium bromide to the ester.* Certain of the experiments [Table 5(*a*)] were repeated, an equivalent of magnesium bromide being mixed with the ester solution before its addition to the Grignard reagent. The results are shown in Table 5(*c*).

(d) *Other products.* In the above experiments careful fractionation was required to separate the various products, the boiling points of which often differed by small amounts only (*e.g.*, excess of ester, ketone, and the secondary alcohol). The yields given are thus only the minimum yields, since handling losses in such distillations are necessarily high. Chemical means were used to separate ethyl heptafluorobutyl ketone from traces of ethyl alcohol (distillation; P_2O_5) and heptafluoroheptan-4-ol from ethyl butyrate (hydrolysis, then distillation). In experiments with the fluoro-esters the material of boiling point higher than that of the *tert.*-alcohols decomposed on attempted distillation, with the formation of ethyl alcohol and small amounts of the perfluoro-ketones. Precise identification of these possible hemiacetals was not achieved.

The Reaction of Methyl-, Ethyl-, and Propyl-magnesium Iodides with Ethyl Heptafluorobutyrate, Trifluoroacetaldehyde, Heptafluorobutyraldehyde and Heptafluoropentan-2-one.—(a) *Compounds added to the Grignard reagent.* To methylmagnesium iodide (from 8·0 g. of methyl iodide) in ethyl ether (120 ml.) was added ethyl heptafluorobutyrate (4·8 g.) in ethyl ether (30 ml.) during 5 hr., and the mixture stirred for 1 hr. 3 : 3 : 4 : 4 : 5 : 5 : 5-Heptafluoro-2-methylpentan-2-ol (70%), b. p. 105—107° (see Part I), was obtained, but no 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol.

Ethylmagnesium iodide (from 8·8 g. of ethyl iodide) under similar conditions gave 4 : 4 : 5 : 5 : 6 : 6 : 6-*heptafluoro-2-ethylhexan-3-ol* (15%), b. p. 144—146° (Found: C, 37·2; H, 4·7%. $C_8H_{11}OF_7$ requires C, 37·5; H, 4·3%), and 4 : 4 : 5 : 5 : 6 : 6 : 6-heptafluorohexan-3-ol (62%) (see above). Infra-red spectroscopic examination showed ethylene to be a product.

Trifluoroacetaldehyde (3·0 g.), passed into methylmagnesium iodide (from 8·0 g. of methyl iodide) during 5 hr. with conditions as above, gave 3 : 3 : 3-trifluoropropan-2-ol (65%), and only a trace of trifluoroethanol could be detected.

n-Propyl iodide (8·0 g.) was converted into propylmagnesium iodide and similarly treated with trifluoroacetaldehyde, giving trifluoroethanol (77%) and 5 : 5 : 5-trifluoropentan-4-ol (5%; from three similar experiments), b. p. 110—112°. Campbell, Knobloch, and Campbell (*loc. cit.*) report b. p. 109—111°/745 mm. Propylene (identified by its infra-red spectrum) was formed in 58% yield.

Heptafluorobutyraldehyde (4·0 g.) similarly added to propylmagnesium iodide solution gave heptafluorobutanol (72%), 5 : 5 : 6 : 6 : 7 : 7 : 7-heptafluoroheptan-4-ol (8%), and propylene (42%).

Methylmagnesium iodide was prepared from methyl iodide (6·0 g.), and to the filtered solution was added heptafluoropentan-2-one (4·2 g.) in ethyl ether (20 ml.) during 3 hr.; 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoro-2-methylpentan-2-ol (71%) (see Part I, *loc. cit.*) was obtained but no 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol.

Ethyl iodide (6·5 g.) was converted into the Grignard reagent, which was similarly treated with the heptafluoropentanone and gave 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol (59%) and 4 : 4 : 5 : 5 : 6 : 6 : 6-heptafluoro-3-methylhexan-3-ol (14%), b. p. 124—126° (Found: C, 34·4; H, 4·0%. Calc. for $C_7H_9OF_7$: C, 34·7; H, 3·7%). McBee *et al.* (*loc. cit.*) report b. p. 125° for the tertiary alcohol.

(b) *Addition of Grignard reagent to an excess of the compound.* The experiments with ethyl heptafluorobutyrate, were repeated, but only 80% of the alkylmagnesium iodide theoretically required to give the *tert.*-alcohol was used. The filtered ethereal solution of the Grignard reagent was added to the ester in ethyl ether (10 ml.) during 3 hr. Methylmagnesium iodide gave the tertiary alcohol (51%) and 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-one (5%), but no secondary alcohol. With ethylmagnesium iodide the tertiary alcohol (8%), secondary alcohol (45%), and 4 : 4 : 5 : 5 : 6 : 6 : 6-heptafluorohexan-3-one (10%) were isolated.

(c) *Addition of magnesium bromide.* Magnesium bromide (4·0 g.) was added to heptafluorobutyraldehyde (4·0 g.) dissolved in ether (75 ml.) and, after 10 min., propylmagnesium iodide (from 8·0 g. of propyl iodide) was added during 3 hr., the total volume of solvent being the same as in (a). Heptafluorobutanol (39%) and 5 : 5 : 6 : 6 : 7 : 7 : 7-heptafluoroheptan-4-ol (33%) were obtained.

In another experiment, the fluoro-aldehyde and magnesium bromide solution was added to the propylmagnesium iodide solution. The products were heptafluorobutanol (46%) and 5 : 5 : 6 : 6 : 7 : 7 : 7-heptafluoroheptan-4-ol (26%).

Heptafluoropentan-2-one was mixed with magnesium bromide (4·0 g.) in ethereal solution and, with conditions otherwise the same as in (a) above, was added to methylmagnesium iodide solution. The product was 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoro-2-methylpentan-2-ol (66%), and 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol was not detected.

Similar reaction with ethylmagnesium iodide gave **4 : 4 : 5 : 5 : 6 : 6 : 6**-heptafluoro-3-methylhexan-3-ol (37%) and **3 : 3 : 4 : 4 : 5 : 5 : 5**-heptafluoropentan-2-ol (22%).

Addition of Grignard solution to the ketone–magnesium bromide solution gave tertiary (35%) and secondary alcohol (26%).

Preparation of Secondary Alcohols by Reduction of Ketones.—A solution of the ketone (0·01 mole) in diethyl ether (10 ml.) was slowly added to one of lithium aluminium hydride (0·02 mole) in diethyl ether (10 ml.), stirred vigorously and cooled in ice. After the temperature had slowly risen to boiling point, water and then sulphuric acid were added, and the dried ethereal extracts were distilled. The yields of secondary alcohols obtained were :

Ketone ...	C_3F_7·COMe *	C_3F_7·COEt	C_3F_7·COPr	C_3F_7·CO·CF_3 *	C_3F_7·CO·C_2F_5 *	C_3F_7·CO·C_3F_7
Alcohol, %	67	71	62	61	69	83

* *n*-Butyl ether as solvent.

Oxidation of Certain Secondary Alcohols.—The following general procedure was used for the oxidation of 1-(perfluoropropyl)alkanols to the corresponding ketones. To the alcohol (0·02 mole) and 80% sulphuric acid (3 ml.) was added a solution of potassium dichromate (5 g.) in water (10 ml.) and concentrated sulphuric acid (4 ml.) as fast as was consistent with the temperature remaining below 80°. The ketone was then removed to a vacuum system and purified by fractionation. The yields of heptafluoropentan-2-one, heptafluorohexan-3-one, and heptafluoroheptan-4-one were 71, 75, and 68%, respectively.

Action of Alkali on Alkylheptafluoropropylketones.—The ketone C_3F_7·COR (R = Me, Et, Pr, or C_3F_7) (0·2 g.) was sealed with 5% aqueous sodium hydroxide (5 ml.) at room temperature for 36 hr. The yields of heptafluoropropane, identified spectroscopically (Part I, *loc. cit.*), were 81, 86, 83, and 88%, respectively.

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362. *Studies in Spectroscopy. Part II.* The Ionisation Constants and Infra-red Spectra of Some Primary and Secondary Halogen-containing Alcohols.*

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The primary alcohols R·CH_2·OH (R = perfluoroalkyl, CHF_2·CF_2, CHF_2·$[CF_2]_3$, CHF_2, CF_2Cl or CCl_3) and the secondary alcohols CHRR′·OH (R = perfluoroalkyl, R′ = alkyl) have ionisation constants some 10^4 greater than their hydrocarbon analogues. When both R and R′ are perfluoroalkyl a further 10-fold increase in acidity is observed. The infra-red spectra of these alcohols, and of certain chlorine-containing alcohols, in the 3-μ region reveal the effect of hydrogen bonding. Intermolecular hydrogen bonding is much reduced and is almost non-existent in the secondary polyhalogeno-alcohols; intramolecular hydrogen bonding of the O–H···X type is considered.

THE synthesis of perfluoro-*sec.*-alcohols (preceding paper) enables the effect of introducing halogen, particularly fluorine, into primary and secondary aliphatic alcohols on ionisation constants and hydrogen bonding to be measured.

The ionisation constants of a series of primary and secondary alcohols are recorded in Table 1. It is emphasised that the figures are not absolute values suitable for quantitative comparison with those obtained in aqueous solution, and that they are open to the errors outlined in the Experimental section. They serve, however, to compare the acid strengths of the various alcohols against each other in the particular solvent used (50% aqueous ethanol).

For the primary alcohols, comparison of ethanol (R = Me; $K = 3 \times 10^{-16}$; Denner and Hildebrand, *J. Amer. Chem. Soc.*, 1922, **44**, 2824) with trifluoroethanol shows that replacement of hydrogen by fluorine causes an increase in acidity in the ratio of $\sim 10^4$, in agreement with investigations by McBee, Marzluff, and Pierce (*ibid.*, 1952, **74**, 444), and

* Part I, *J.*, 1952, 3284.

Henne and Pelley (*ibid.*, p. 1426) (cf. Swarts, *Bull. Soc. chim. Belg.*, 1929, **38**, 99, who reported $K = 10^{-7}$).

The trifluoromethyl group contains three electronegative fluorine atoms bound to carbon and should, if the inductive effect is all-important, be more electron-attracting than,

TABLE 1. *Approximate* pK_a *values of primary alcohols,* $R{\cdot}CH_2{\cdot}OH$, *and secondary alcohols,* in 50% alcohol.*

R	CF_3	C_2F_5	C_3F_7	C_4F_9	C_5F_{11}	C_7F_{15}	CCl_3
pK_a	11·32	11·35	11·36	11·35	11·37	11·35	11·80
$10^{12}K$	4·8	4·5	4·4	4·5	4·3	4·5	1·6

R	CHF_2	CF_2Cl	$CHF_2{\cdot}CF_2$	$CHF_2{\cdot}(CF_2)_3$	$CF_3{\cdot}CH_2$	$CF_3{\cdot}(CH_2)_2$
pK_a	12·00	11·62	11·34	11·35	12·7	12·9
$10^{12}K$	1·0	2·4	4·6	4·5	0·2 †	0·1 †

	$CF_3{\cdot}CHMe{\cdot}OH$	$C_3F_7{\cdot}CHMe{\cdot}OH$	$C_3F_7{\cdot}CHEt{\cdot}OH$	$C_3F_7{\cdot}CHPr{\cdot}OH$
pK_a	11·28	11·38	11·37	11·37
$10^{12}K$	5·2	4·2	4·3	4·3

	$C_3F_7{\cdot}CH(CF_3){\cdot}OH$	$C_3F_7{\cdot}CH(C_2F_5){\cdot}OH$	$(C_3F_7)_2CH{\cdot}OH$
pK_a	10·46	10·48	10·52
$10^{12}K$	35	33	30

* Values for secondary alcohols presented at the Amer. Chem. Soc. Meeting, Atlantic City, September, 1952. † These values are probably high; see below.

say, C_2F_5 or C_3F_7 formed by replacement of a fluorine atom by a less electronegative perfluoroalkyl group. On this basis one would predict that trifluoroacetic acid is an acid appreciably stronger than pentafluoropropionic acid, and that little difference in acid strength will be detected (by refined technique in non-aqueous media) in the series $R_F{\cdot}CO_2H$ ($R_F = C_2F_5$, C_3F_7, C_4F_9, etc.), since although passage from pentafluoropropionic to heptafluorobutyric acid also involves replacement of a fluorine atom by a less electronegative trifluoromethyl group, the difficultly polarised CF_2 group adjacent to the carbonyl group will effectively shield changes in the β-position. It can similarly be predicted that the alcohol $R{\cdot}CH_2{\cdot}OH$ where $R = CF_3$ would be a stronger acid than that with $R = C_2F_5$, and that little change should be apparent for $R = C_3F_7$, C_4F_9, etc., or for $R = R'{\cdot}CF_2{\cdot}CF_2$, where R′ is a group not necessarily containing fluorine. The accuracy of the method used for the determination of K is such that only a value $4—5 \times 10^{-12}$ can be given for alcohols where $R = R'{\cdot}CF_2{\cdot}CF_2$, but there is some indication that K is higher when $R = CF_3$ than in the other examples (see also the secondary alcohols).

The pK_a values for $CF_3{\cdot}(CH_2)_2{\cdot}OH$ and $CF_3{\cdot}(CH_2)_3{\cdot}OH$ are probably appreciably higher than recorded in Table 1, since the experimental method becomes insensitive in this region. The results, however, show the marked decrease in K on changing from $CF_3{\cdot}CH_2{\cdot}OH$ to $CF_3{\cdot}(CH_2)_n{\cdot}CH_2{\cdot}OH$, and this is attributed to the large difference in inductive effect between a CF_3 group and a $CF_3{\cdot}CH_2$ or $CF_3{\cdot}(CH_2)_2$ group (cf. $CF_3{\cdot}CO_2H$, $CF_3{\cdot}CH_2{\cdot}CO_2H$, $CF_3{\cdot}(CH_2)_2{\cdot}CO_2H$; Henne and Fox, *J. Amer. Chem. Soc.*, 1951, **73**, 2323).

The values of K for primary alcohols where $R = CCl_3$, CHF_2, and CF_2Cl are comparable and, as expected, are appreciably less than when R = perfluoroalkyl. It is noteworthy that trifluoroethanol is not more than ten times more acidic than trichloroethanol.

In secondary alcohols containing only one perfluoroalkyl group, $K = 4—5 \times 10^{-12}$, as for the primary alcohols, and the inductive effect of the perfluoroalkyl group far outweighs that of the opposing alkyl group. Introduction of a second perfluoroalkyl group causes a marked increase in acid strength, however, with $K = 3 \times 10^{-11}$, although the effect is only one-thousandth of that caused by introduction of the first perfluoroalkyl group into methanol. The value of K for the secondary perfluoro-alcohols agrees with their failure to liberate carbon dioxide from sodium carbonate solution (*i.e.*, $K < 10^{-10}$), although they are much more soluble in dilute sodium hydroxide solution than in water. It thus appears that maximum polarisation of the OH group is almost achieved by introduction of the first perfluoroalkyl group, and the ionisation constant of a tertiary perfluoro-alcohol should thus be only slightly larger than that of a secondary one. Results will be presented

later to show that this is so. An important factor here is the absence of important resonance stabilisation of the secondary perfluoro-alkoxide ion which could cause spread of the charge from oxygen; thus, the inductive effect of an R_2CH (R = perfluoroalkyl) group is greater than that for phenyl, yet phenol ($K = 1 \times 10^{-10}$) is comparable in acidity with the secondary perfluoro-alcohols, since resonance effects involving structures of the ion such as O=⬡- or O=⬡ lead to greater ionisation. A perfluorophenol, where both inductive and resonance effects can operate, should thus be much stronger than phenol.

The lower basicity of the oxygen atom with increasing fluorine content of the molecule is shown by boiling-point and infra-red measurements. Table 2 indicates that intermolecular hydrogen bonding decreases with increase in fluorine content of a secondary alcohol.

TABLE 2. *B. p.s of* CHRR'·OH.

R	Pr	Pr	Pr	C_3F_7	C_3F_7	C_3F_7	C_3F_7	C_3F_7	C_3F_7
R'	Me	Et	Pr	Me	Et	Pr	CF_3	C_2F_5	C_3F_7
B. p.	119	135	155	101	114	128	50/210 mm.	61/150 mm.	70/103 mm.

The solubility of secondary perfluoro-alcohols in water or concentrated sulphuric acid decreases with increase in molecular weight, as it does for perfluoro-carboxylic acids, and perfluorohexan-3-ol is substantially insoluble in these solvents.

It is well established that the vapour of an alcohol, or dilute solutions of the alcohol in a solvent such as carbon tetrachloride, show a sharp infra-red absorption band at *ca.* 2·75 μ which is characteristic of the non-hydrogen-bonded hydroxyl group (" free " hydroxyl group), and that an alcohol in the pure liquid or solid state, or in concentrated solution in carbon tetrachloride, will show a broad band at *ca.* 3 μ characteristic of the intermolecularly hydrogen-bonded hydroxyl group (" bonded " hydroxyl group) (see, *e.g.*, Fox and Martin, *Proc. Roy. Soc.*, 1937, *A*, **162**, 419). The infra-red spectra of the series of halogen-containing alcohols have therefore been investigated in the 1—4-μ region in solution and in the pure state, and provide qualitative information of the extent of hydrogen-bonding.

Intermolecular Hydrogen Bonding.—The wave-lengths of the bands under discussion are shown in Table 3. Data for ethyl and *iso*propyl alcohol are included for comparison. The spectra are of three main types, shown in Figs. I—III.

The liquid polyfluoro-alcohols $R{\cdot}CH_2{\cdot}OH$ (R = CF_3, C_2F_5, C_3F_7, $CHF_2{\cdot}CF_2$, $CHF_2{\cdot}[CF_2]_3$, CHF_2) show similar spectra which closely resemble those of unsubstituted alcohols, with a broad, strong band of the bonded-OH group near 3 μ (Fig. I*a*). Some indication of reduced hydrogen bonding relatively to unsubstituted alcohols is given by the weak but definite free-OH peak at *ca.* 2·75 μ on the side of the bonded OH band, since unsubstituted alcohols show only a very slight inflection at this point. When R = CHF_2 or $CF_3{\cdot}CH_2$, the 2·75-μ band appears as a pronounced inflection. The bonded-OH band is much reduced in intensity when the primary polyfluoro-alcohols are dissolved in carbon tetrachloride and is shifted to 2·87—2·91 μ; the free-OH band at 2·77—2·78 μ is sharp and its intensity relative to the bonded-OH group increases with increasing dilution, until finally the bonded-OH group disappears. The OH overtone band appears at 1·49 μ (Figs. I*b*, *c*, and *d*).

By using comparable concentrations (0·05—0·1M) of the alcohols in which R = Et, CF_3, and $CHF_2{\cdot}CF_2$, a difference in hydrogen bonding can be detected, since the relative intensity of the bonded-OH band to the free-OH band is less when R = CF_3 or $CHF_2{\cdot}CF_2$ than when R = Et.* The concentrations used are limited by the low solubility of the fluoro-alcohols in carbon tetrachloride, so that comparisons have to be made when the bonded-OH band has only a moderate intensity (Fig. I*c*). The decrease in intermolecular hydrogen bonding is, however, more effectively shown by comparison of ethanol and trichloroethanol, since the latter is readily soluble in carbon tetrachloride. At 0·2M concentration ethanol has a spectrum of contour Fig. I*b*, *i.e.*, the bonded-OH group

* A Referee has kindly pointed out that this assumes that halogen substitution in the alcohol has much the same effect on the extinction coefficients of the two bands.

predominates, but with identical concentration trichloroethanol has spectrum Fig. Ic *i.e.*, the free-OH group predominates. Pure trichloroethanol shows an inflection at 2·75 μ, with the bonded-OH band at 3·03 μ.

The ultra-violet spectroscopic results (Table 4) are of interest in connection with the basicity of oxygen in polyhalogeno-alcohols.

Kleinberg and Davidson (*Chem. Reviews*, 1948, **42**, 601) quote literature values of 480 mμ for a solution of iodine in EtOH and 540 mμ for that in CCl_4. Benesi and

TABLE 3. *Infra-red spectra of halogenated alcohols in the 1—4-μ region.*

(a) *Primary alcohols*, $R{\cdot}CH_2{\cdot}OH$.

	Pure compound.		CCl_4 solutions.		
			Conc. solution.		Effect of dilution
R	Bonded OH	Free OH	Bonded OH	Free OH	
CF_3 [1]	2·99 (b.s.)	2·77 (w.si)	2·87 (b.m.)	2·77 (sh.s.) 1·49 (sh.vw.)	
C_2F_5 [1]	2·99 (b.s.)	2·78 (w.si)	2·88 (b.m.)	2·78 (sh.s.) 1·49 (sh.vw.)	
C_3F_7 [1]	3·00 (b.s.)	2·79 (w.si)	2·89 (b.m.)	2·78 (sh.s.) 1·49 (sh.vw.)	
$CHF_2{\cdot}CF_2$ [1]	3·03 (b.s.)	2·8 (w.si)	2·88 (b.m.)	2·77 (sh.s.) 1·49 (sh.vw.)	Bonded OH band vanishes on high dilution
$CHF_2{\cdot}[CF_2]_3$ [1]	3·01 (b.s.)	2·75 (w.si)	2·91 (b.m.)	2·78 (sh.s.) 1·49 (sh.vw.)	
CHF_2 [2]	3·02 (b.s.)	2·75 (infl.)	3·0 (b.s.)	2·78 (sh.m.) 1·49 (sh.vw.)	
$CF_3{\cdot}CH_2$ [2]	3·02 (b.s.)	2·75 (infl.)	3·0 (b.s.)	2·78 (sh.m.) 1·49 (sh.vw.)	
CCl_3 [3]	3·03 (b.s.)	2·75 (infl.)	2·91 (b.s.)	2·80 (sh.s.) 1·49 (sh.vw.)	Bonded OH 2·87 and disappears on dilution. Free OH 2·78
$CH_2{\cdot}CH_2$	3·01 (b.s.)	—	3·0 (b.s.)	2·75 (sh.m.) 1·46 (sh.vw.)	Bonded OH vanishes on high dilution

(b) *Secondary alcohols.*

	Pure compound		CCl_4 solutions		
			Conc. solution		Effect of dilution
Alcohol	Bonded OH	Free OH	Bonded OH	Free OH	
$CF_3{\cdot}CHMe{\cdot}OH$ [1] ...	2·98 (b.s.)	2·8 (w.infl.)	2·92 (b.m.)	2·76 (sh.s.) 1·47 (sh.vw.)	
$C_2F_7{\cdot}CHMe{\cdot}OH$ [2] ...	2·98 (b.s.)	2·8 (w.infl.)	2·29 (b.m.)	2·77 (sh.s.) 1·47 (sh.vw.)	Bonded OH band vanishes
$C_3F_7{\cdot}CHPr{\cdot}OH$ [2] ...	2·98 (b.s.)	2·79 (w.infl.)	2·91 (b.m.)	2·78 (sh.s.) 1·49 (sh.vw.)	
PrOH	3·01 (b.s.)	—	3·00 (b.s.)	2·75 (sh.m.) 1·46 (sh.vw.)	
$(CCl_3)_2CH{\cdot}OH$ [3]	2·9 (s.)	2·82 (sh.s.)	—	2·79, 2·83 (sh.s. doublet) 1·50 (sh.vw.)	No change in relative intensity
$CCl_3{\cdot}CH(C_2Cl_5){\cdot}OH$ [3]	2·95 (s.)	2·86 (sh.s.)	—	2·80, 2·85 (sh.s. doublet) 1·5 (sh.vw.)	
$C_3F_7{\cdot}CH(C_2F_5){\cdot}OH$ [1]	2·90 (m.)	2·78 (sh.s.)	—	2·76 (w.si.) 2·79 (sh.s.) 1·5 (sh.vw.)	No change in relative intensity
$(C_3F_7)_2CH{\cdot}OH$ [1] ...	2·89 (m.)	2·79 (sh.s.)	—	2·76 (w.si) 2·79 (sh.s.) 1·5 (sh.vw.)	

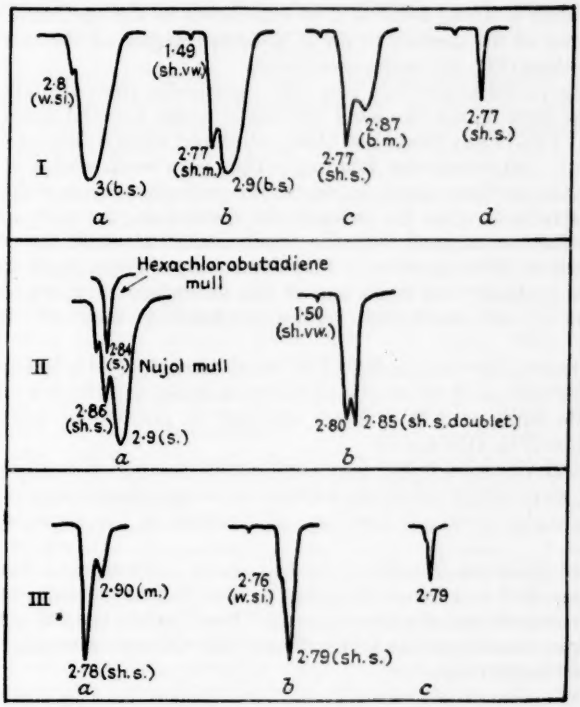
[1] Low solubility in CCl_4. [2] Moderate solubility in CCl_4. [3] Very soluble in CCl_4.
b. = broad; infl. = inflection; m. = medium; s. = strong; sh. = sharp; si. = side-band; vw. = very weak; w. = weak.

TABLE 4. *Ultra-violet spectra of iodine in various solvents.*

Solvent	EtOH	$CHF_2{\cdot}CF_2{\cdot}CH_2{\cdot}OH$	$CCl_3{\cdot}CH_2{\cdot}OH$	CCl_4
$\lambda_{max.}$, mμ	444	490	500	516

Hildebrand (*J. Amer. Chem. Soc.*, 1949, **71**, 2703) report 517 mμ for CCl_4 solutions. Mulliken (*J. Amer. Chem. Soc.*, 1950, **72**, 600) attributed the shift in maximum from carbon tetrachloride to ethanol solutions to complex formation of the acid–base type in which iodine acts as an electron-acceptor, and an electron of the lone pair of the oxygen atom is partly transferred to the iodine. The long-wave-length maximum for iodine in the alcohols where R = CCl_3 or $CHF_2{\cdot}CF_2$ is displaced to the visible region relatively to that in ethanol, as would be expected for decreased basicity of oxygen. The solution of iodine in the chloro-alcohol unexpectedly resembles that in carbon tetrachloride more than does that in the fluoro-alcohol; this is possibly correlated with the much higher solubility of iodine in a polychloro-compound such as carbon tetrachloride than in a polyfluoro-compound such

Infra-red spectra of halogeno-alcohols in the 3-μ region.



(*a*) *Pure compound.* (*b, c, d*) CCl_4 *solutions of decreasing concentration. See footnotes to Table* 3 *for abbreviations.*

as a fluorocarbon, or it may indicate steric hindrance of complex formation in the chloro-alcohol.

In assessing the change in intermolecular hydrogen bonding on introduction of halogen into an alcohol, two opposing factors are involved: reduction in the basicity of the oxygen atom will reduce the strength of the hydrogen bond in which this oxygen acts as electron donor, but the increase in acidity of the alcohol revealed by the ionisation constant data, *i.e.*, increases in the effective positive charge on the hydrogen atom, will lead to an increase in the strength of the hydrogen bond in which the acidic hydrogen atom participates. The first of these effects apparently predominates in the primary polyhalogeno-alcohols, since intermolecular hydrogen bonding is reduced relatively to that in the hydrocarbon analogues.

The secondary alcohols R·CH(OH)Alkyl (R = perfluoroalkyl) show a free-OH band at 2·8 μ (inflection) in their infra-red spectra, but the bonded-OH band still predominates

(Fig. I*a*); the spectra in solution are similar to those of the primary halogen-containing alcohols (Fig. I*b*—*d*), and indicate reduced hydrogen bonding relatively to that in *iso*-propyl alcohol.

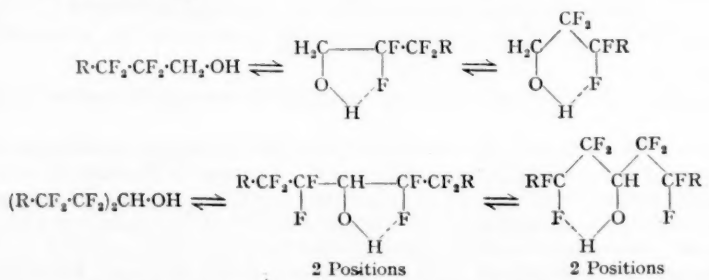
The secondary polyhalogeno-alcohols show a marked change. 1 : 1 : 1 : 3 : 3 : 3-Hexachloropropan-2-ol in Nujol suspension shows a strong band at 2·9 μ which is much sharper than that normally observed for the bonded-OH group; 1 : 1 : 1 : 3 : 3 : 4 : 4 : 4-octachlorobutan-2-ol similarly shows a band at 2·95 μ with a free-OH band at 2·86 μ (Fig. II*a*). The intermolecular hydrogen bonding is extremely weak, since, even though the alcohols are readily soluble in carbon tetrachloride, the most concentrated solution fails to show a band in the 2·9—3·0-μ region. That the weak intermolecular hydrogen bonds are broken as soon as the alcohols dissolve is also shown by use of hexachlorobutadiene as suspending medium instead of Nujol, since the alcohols partly dissolve in the chloro-diene and only a strong band at 2·84 μ is shown in the spectrum (Fig. II*a*). The possible significance of the doublet in the 2·79—2·85-μ region of the spectrum for carbon tetrachloride solutions (Fig. II*b*) is discussed below.

The secondary perfluoro-alcohols also differ markedly from the alkylperfluoroalkylcarbinols. In the pure liquids the band attributed to the free-OH group (2·78 μ) is very strong and that at 2·9 μ is only weak (Fig. III*a*); the latter band is sharper than for the usual bonded-OH group. Intermolecular bonding is thus very weak, and it is noteworthy that the change with the perfluoro-alcohols, where the ionisation constant has been increased only 10-fold relatively to that for primary fluoro-alcohols, is much greater than that observed for the latter compared with the unsubstituted alcohols, for which a change in ionisation constant of 10^4 is involved. Fluorine is only slightly larger than hydrogen, so steric factors are probably not important in the secondary perfluoro-alcohols, although steric inhibition of intermolecular hydrogen bonding may be involved in the chloro-alcohols.

In solution (limited by the solubility) no band attributed to a bonded-OH group can be observed in the spectra of secondary perfluoro-alcohols, and the free-OH band at 2·79 μ with a weak side band at 2·76 μ is not changed in position or relative intensity by subsequent dilution (Fig. III*b* and *c*).

The bonded-OH vibration in the pure compounds recorded in Table 3 shows a distinct trend to shorter wave-length relatively to that for unsubstituted alcohols, also indicating reduced intermolecular hydrogen bonding, particularly in the secondary polyhalogeno-alcohols.

Intramolecular Hydrogen Bonding.—In the above discussion, a band at *ca.* 2·75—2·80 μ has been ascribed to a "free OH group." The hydroxyl group producing a band at this position in unsubstituted alcohols is clearly "free," but in the halogeno-alcohols intramolecular hydrogen bonding of the O–H····F or O–H····X type is possible, with formation of five- or six-membered rings:



The evidence at present available suggests that hydrogen bonding of this type can occur in the polyhalogeno-alcohols but is not strong. The "free"-hydroxyl bands observed in carbon tetrachloride solutions are at slightly longer wave-lengths (2·77—2·79 μ) than those observed in parallel experiments with solutions of unsubstituted alcohols (EtOH, 2·75; Pr^iOH, 2·75; Bu^tOH, 2·76 μ). This shift is small but definite, and in absence of

more detailed studies with a prism of higher resolving power may be ascribed either to the effect of the adjacent polyhalogeno-group or groups on the stretching vibration of the free hydroxyl group, or to intramolecular hydrogen bonding of the O–H···X type. If intramolecular hydrogen-bonding is occurring, then the doublet observed in the carbon tetrachloride solution spectra of the chloro-alcohols, and possibly the weak side band in the solution spectra of the secondary perfluoro-alcohols, may be significant, since the peaks at lower wave-length [$(CCl_3)_2CH{\cdot}OH$ 2·79, $CCl_3{\cdot}CH(C_2Cl_5){\cdot}OH$ 2·80, $C_3F_7{\cdot}CH(C_2F_5){\cdot}OH$ *ca.* 2·76, $(C_3F_7)_2CH{\cdot}OH$ *ca.* 2·76] could be ascribed to a truly free hydroxyl group and the stronger bands of the doublet (Table 3) to the O–H···X bonded hydroxyl group. The overtone hydroxyl group band is also at longer wave-length (1·49—1·50 μ) than that in hydrocarbon alcohols (1·46—1·47 μ), but the fact that it appears at all in carbon tetrachloride solution shows that the intramolecular hydrogen bonding is not strong, *i.e.*, resembles the bonding in *o*-chlorophenol rather than that in *o*-nitrophenol.

Experimental

Determination of Ionisation Constant.—A convenient and rapid method for determination of ionisation constant is that used by Bennett, Brooks, and Glasstone (*J.*, 1935, 1821), involving determination of pH at the half-neutralisation point and application of the Henderson equation $pH = pK_a$. This gives accurate results for the range 4—10, but for pH >10·5 errors caused by hydrolysis arise (Glasstone, "Electrochemistry of Solutions," Methuen, 1945, pp. 218—222). To keep such errors as low as possible, fairly concentrated solution (0·1N) in 50% aqueous ethanol were used where possible. This solvent is convenient, since (*a*) not all the alcohols studied are sufficiently soluble in water to enable comparable concentrations to be used throughout, and (*b*) K_w for 50% aqueous ethanol will be in the range 10^{-16}—10^{-14} compared with 10^{-14} for water, and hydrolysis errors will be reduced (see equations in Glasstone, *op. cit.*).

The alcohols were mainly samples prepared in these laboratories (Haszeldine, *J.*, 1952, 3423; 1950, 2789; preceding paper; *Nature*, 1950, **166**, 192; 1951, **168**, 1028; Haszeldine and Leedham, *J.*, 1953, 1548) and stored in sealed ampoules before use. The compounds $CCl_3{\cdot}CHR{\cdot}OH$ (R = CCl_3, C_2Cl_5) were kindly supplied by CIBA Ltd., Switzerland (see Geiger, Usteri, and Granacher, *Helv. Chim. Acta*, 1951, **34**, 1335). W. C. Francis and A. L. Henne have recently reported (personal communication) that *K* for $(C_3F_7)_2CH{\cdot}OH$ is $2{\cdot}2 \times 10^{-11}$.

Solutions were made up by weight, and volumetric apparatus was calibrated before use. Portions (5, 10, or 20 ml.) of the alcohol solution were titrated against carbonate-free 0·1N-sodium hydroxide in the same solvent. The pH at the half-neutralisation point was measured by a Cambridge Instrument Co. meter fitted with an Alki-Glass or Doran sealed-glass electrode for the pH range 10—13, and standardised against a series of buffers. Two determinations were made with each alcohol. A control experiment with phenol gave $K = 0{\cdot}8 \times 10^{-10}$ in water (lit., 1×10^{-10}), and $K = 0{\cdot}4 \times 10^{-10}$ in 50% aqueous ethanol. Bennett *et al.* (*loc. cit.*) have shown that the order of strengths of a series of weak acids is the same in 30% aqueous ethanol as in water, although the p*K* values are 0·3—0·5 unit higher than in water.

The accuracy of the results summarised in Table 1 is probably $\gtrsim 0{\cdot}5 \times 10^{-12}$ for ionisation constants 1—10×10^{-12}, with a somewhat greater accuracy for the secondary perfluoro-alcohols. The method is insensitive for $K < 1 \times 10^{-12}$, and results in this region are probably high.

Infra-red Spectra.—A Perkin–Elmer Model 21 Double Beam Instrument with sodium chloride optics was used. Wave-lengths are accurate to ±0·01 μ. The spectra of the pure compounds were examined either as a liquid film (0·025 mm. thick), or as a suspension in Nujol or hexachlorobutadiene. Moisture was carefully excluded. The spectra of carbon tetrachloride solutions were taken in 1·0- or 3·0-mm. cells. Solutions were made up approximately, at concentrations from 0·05 to 0·5M depending on solubility, or, if a compound was only slightly soluble, a saturated solution was used. Dilutions were made from the parent solutions.

Ultra-violet spectra were determined on a Unicam Spectrometer, 1-cm. silica cells being used.

Grateful acknowledgment is made to CIBA Ltd., Switzerland, for the gift of two of the compounds used in this investigation.

University Chemical Laboratory, Cambridge. [*Received, December 16th*, 1952.]

363. *Studies in Spectroscopy. Part III.* The Ultra-violet Absorption Spectra of Halogen-containing† Aliphatic Iodo-compounds, and the Relative Stability of Free Halogen-containing Alkyl Radicals.*

By R. N. Haszeldine.

The ultra-violet spectra of a variety of organic iodo-compounds of the type $\overset{\beta}{C}-\overset{\alpha}{C}\cdot I$ with various combinations of H, F, Cl, Br, and I substituted on the α, β, or γ carbon atom have been determined; the spectra of compounds of type $I\cdot[\overset{\vee}{C}-\overset{\vee}{C}]_n\cdot I$, and of some secondary and tertiary iodides have also been recorded. The position of the near ultra-violet maximum, which is very sensitive to structural change and to substitution on the β- and, particularly, on the α-carbon atom, varies from 257 mμ for a *n*-alkyl iodide to 346 mμ for CBr_3I, and can be used diagnostically for unknown iodo-compounds. Bathochromic shifts of the maxima increase in the order of substituents H < F < Cl < Br < I. Interaction between the carbon–iodine chromophores can be detected in $I\cdot[CH_2]_n\cdot I$ and $I\cdot[CF_2]_n\cdot I$ when $n = 2$, but not when $n \geqslant 3$. The auxochromic effect of halogen on the carbon–iodine chromophore is discussed.

The stabilisation of alkyl radicals by halogen substitution, and steric effects in molecules of type $-CX_2I$ and $-CX_2Br$, are considered and, by qualitative correlation of radical stability with position of the absorption maximum, relative stabilities for primary, secondary, and tertiary alkyl and halogenoalkyl radicals are proposed.

In connection with work on organic halogen compounds reported elsewhere, the ultra-violet spectra of a variety of iodo- and polyhalogeno-iodo-compounds† have been examined, and the position of the characteristic broad absorption maximum in the 250—350-mμ region has been correlated with structure.

The discussion below refers to solutions of the compounds in light petroleum or to vapour spectra, since the polyhalogeno-iodo-compounds show marked solvent effects (which will be discussed later); if the spectrum is only slightly affected by change of solvent from light petroleum to ethanol, values in both solvents are given.

Alkyl Iodides: $R\cdot[CH_2]_n\cdot I$, $R'R''CH\cdot[CH_2]_m\cdot I$, R_3CI, $I\cdot[CH_2]_x\cdot I$.—The values in Table 1(*a*) show that compounds $R\cdot[CH_2]_n\cdot I$ are characterised by a maximum at 257 mμ (ε 400—500), and a minimum at 210—215 mμ (ε <50). There is only a slight shift of wave-length (2—4 mμ) on change to ethanol, and the continuum is broad with a well-defined maximum.

For $R'R''CH\cdot[CH_2]_m\cdot I$ [Table 1(*b*)], chain branching has but little effect when $m \geqslant 1$, and the spectrum is identical with that of the corresponding compound $R\cdot[CH_2]_n\cdot I$. When $m = 0$, *i.e.*, when the iodine atom is attached to a secondary carbon atom, there is a bathochromic shift of 4 mμ and an increase in intensity of absorption (ε 550—600). *cyclo*Hexyl and *cyclo*pentyl iodide are included as special examples with $m = 0$; steric effects are apparently negligible.

A further bathochromic shift of 7—10 mμ is apparent with solutions of the tertiary iodides R_3CI [Table 1(*c*)], and ε increases to 600—650; a solvent effect of 2—3 mμ is observed on changing from light petroleum to ethanol.

It was difficult to obtain allyl iodide spectroscopically pure, but the spectrum of a freshly distilled sample [Table 1(*d*)] showed a marked increase in absorption relative to a primary alkyl iodide; the absorption maximum is at approximately the position for a tertiary iodide, but ε is enhanced (800—900).

The spectra of the di-iodides $I\cdot[CH_2]_x\cdot I$ [Table 1(*e*)] with $x \geqslant 3$ are very similar to those of $R\cdot[CH_2]_n\cdot I$, with the expected doubled extinction coefficient, and no interaction between the chromophores can be detected. When $x = 2$, however, a shift (3—4 mμ) of the

* Part II, preceding paper. † Used in this sense, halogen excludes iodine.

maximum to longer wave-length with increase in intensity of absorption is apparent, indicating chromophore interaction. When $x = 1$, *i.e.*, when two iodine atoms are attached to the same carbon atom, there is a marked change in spectrum, and a long wave-

TABLE 1.

	Light petroleum solutions				Ethanol solutions			
	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
(*a*) R·$[CH_2]_n$·I.								
MeI	257·5	365	216	30	254·5	360	215	34
	257 *	230	225	30				
EtI	258	435	215	20	255	450	215	28
	258 *	310	215	22				
Pr^nI	258	465	210	15	254·5	485	212	45
Bu^nI	—	—	—	—	255	520	212	45
CH_3·$[CH_2]_4$·I	257·5	500	212	27	255·5	500	212	22
CH_3·$[CH_2]_6$·I	257	300	214	25	254	510	208	33
CH_3·$[CH_2]_7$·I	—	—	—	—	255	500	208	46
CH_3·$[CH_2]_9$·I	—	—	—	—	255	500	208	25
CH_3·$[CH_2]_{11}$·I	—	—	—	—	255	510	209	25
CH_3·$[CH_2]_{15}$·I	257·5	500	210	35	254·5	520	207	70
Cl·$[CH_2]_3$·I	257·5	430	217	60	255	460	214	85
(*b*) R′R″CH·$[CH_2]_m$·I.								
Me_2CH·$[CH_2]_2$·I	257	520	216	27	255	515	217	40
Me_2CH·CH_2I	255·5	510	225	130	254	530	210	125
$CHMe_2I$	261	550	219	24	261	565	227	38
CHMeEtI	261	555	219	24	260	570	220	26
CH_3·$[CH_2]_5$·CHMeI	—	—	—	—	260	580	223	47
cyclo-$C_6H_{11}I$	260	675	222	68	259	710	223	62
cyclo-C_5H_9I	260	540	231	175	257	635	219	375
(*c*) R_3CI.								
Me_2CI	270	590	229	34	268	630	240	150
Me_2EtCI	267	620	228	44	265·5	600	239	223
(*d*) *Allylic iodo-compound.*								
CH_2:CH·CH_2I	271	800	249·5	490	267	900	249·5	700
(*e*) I·$[CH_2]_x$·I.								
x								
1	291·5	1320	260	470	291	1320	260	510
	248	650	235	450	247	670	235	550
2	261	1900	232	725	259·5	1550	232	720
3	258·5	970	223	110	257	1000	224	170
4	257·5	990	217	85	255	1030	217	125
5	256	1020	212	85	255·5	1040	212	95

* Vapour spectra.

length maximum of high intensity ($\varepsilon > 1000$) appears at 291 mμ in addition to a band at 248 mμ (ε *ca.* 600). In $-\overset{\beta}{C}H_2\cdot\overset{\alpha}{C}H_2I$, replacement of hydrogen by iodine on the α-carbon atom thus has the greatest effect.

Fluorine-containing Organic Iodides containing the $-CH_2I$, $>CHI$, $-CH_2$·CHXI, $-CHY$·CHXI, $>CH$·CF_2I, *or* $-CHF$·CF_2I *group* (X *and* Y = *Halogen*).—Fluorine substitution on the γ-carbon atom in $\overset{\gamma}{C}\cdot\overset{\beta}{C}\cdot\overset{\alpha}{C}\cdot I$ causes a well-defined shift of *ca.* 4 mμ, with decrease in intensity relative to a *n*-alkyl iodide [Table 2(*a*)].

Substitution of fluorine on only the β-carbon atom (CF_3·CH_2I) causes a similar shift of 4 mμ, *i.e.*, fluorine has about the same influence on the spectrum in the β- or the γ-position. Substitution of bromine on the β-carbon atom produces a further shift to the red of 4—5 mμ [Table 2(*a*)]. The similarity in position of $\lambda_{max.}$ for vapour and light petroleum solution spectra show that solvent effects in light petroleum are low.

A secondary fluorine-containing alkyl iodide [Table 2(*b*)] shows a bathochromic shift for the $>CHI$ group of 5 mμ with increase in intensity relative to the primary fluorine-containing alkyl iodides of Table 2(*a*), *i.e.*, a structural effect on passing from a primary to

a secondary fluorine-containing iodo-compound similar to that found in the alkyl iodide series. For a secondary iodide $\overset{\gamma}{C}\cdot\overset{\beta}{C}\cdot\overset{\alpha}{C}HMeI$, introduction of fluorine on the γ-carbon causes a distinct shift to the red (6 mμ; cf. MeEtCHI and $CF_3\cdot CH_2\cdot CHI\cdot CH_3$); further substitution of halogen in the methyl group gives an increasing order of bathochromic shifts $CH_2Cl < CF_3 < CF_2Cl$.

The fluoro-iodo-acids reveal the effect of conjugation of the carbon–iodine chromophore with the CO_2Me group [Table 2(*b*)]. Comparison of $CF_3\cdot CH_2\cdot CH_2I$ and

TABLE 2.

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
(*a*) $-CH_2I$.				
$CF_3\cdot CH_2\cdot CH_2I$	261	375	213	20
$CF_3\cdot CH_2I$	262	265	—	—
	262 *	125	215	5
$CF_2Br\cdot CH_2I$	266	420	239	230
	266 *	134	238	60
(*b*) >CHI.				
$CF_3\cdot CH_2\cdot CHI\cdot CF_2Cl$ ...	272	320	227	48
$CF_3\cdot CH_2\cdot CHI\cdot CF_3$	270	290	224·5	26
$CF_3\cdot CH_2\cdot CHI\cdot CH_2Cl$ ...	267	440	216	80
$CF_3\cdot CH_2\cdot CHI\cdot CH_3$	267	430	218	25
$CF_3\cdot CH_2\cdot CHI\cdot CO_2Me$ ...	284	370	252	210
$CF_3\cdot[CH_2\cdot CH\cdot CO_2Me]_2\cdot I$	284	350	252	240
$CH_2I\cdot CO_2H$	279	375	244	175
(*c*) $-CH_2\cdot CHXI$ (X = halogen).				
$CF_3\cdot CH_2\cdot CHFI$.....	262·5	350	218	30
$CF_3\cdot[CH_2\cdot CHF]_2\cdot I$	261	410	221	50
$CF_3\cdot CH_2\cdot CHClI$ ...	277·5	430	231	42
(*d*) $-CHY\cdot CHXI$ (X and Y = halogen).				
$CF_3\cdot CHF\cdot CHClI$ ...	280	400	229	56
(*e*) $>CH\cdot CF_2I$.				
$CF_3\cdot CHMe\cdot CF_2I$ ...	270	330	238	120
(*f*) $-CHF\cdot CF_2I$.				
$CF_3\cdot CHF\cdot CF_2I$ ...	269	255	223	50
	269 *	190	227	23

* For vapour spectra, otherwise in light petroleum solution.

$CF_3\cdot CH_2\cdot CHI\cdot CO_2Me$ shows a bathochromic shift of 23 mμ or, by comparison with a secondary iodide ($CF_3\cdot CH_2\cdot CHMeI$), a shift of 17 mμ. Comparison of the primary iodide, monoiodoacetic acid [Table 2(*b*)], with ethyl iodide reveals a similar shift to the red of 22 mμ.

The spectral properties of a carbon–iodine bond in $\overset{\beta}{C}\cdot\overset{\alpha}{C}-I$ are markedly affected by replacement of hydrogen on the α- or the β-carbon atom by halogen. Introduction of one fluorine atom on the α-carbon atom has little effect, since $CF_3\cdot CH_2\cdot CHFI$, $CF_3\cdot[CH_2\cdot CHF]_2\cdot I$, and $CF_3\cdot CH_2\cdot CH_2I$ have very similar spectra [Table 2(*c*)]. However, chlorine causes a shift to the red of 15 mμ when substituted on the α-carbon atom [Table 2(*c*)]; further introduction of fluorine on the β-carbon atom [$CF_3\cdot CHF\cdot CHClI$; Table 2(*d*)] then causes a further shift to the red of 2—3 mμ.

The only example yet studied of a compound with both α-hydrogen atoms replaced by fluorine but with no halogen substituent on the β-carbon atom [$CF_3\cdot CHMe\cdot CF_2I$; Table 2(*e*)] shows a bathochromic shift of 9 mμ relative to $CF_3\cdot CH_2\cdot CH_2I$ and of 15 mμ relative to *iso*butyl iodide. Replacement of the methyl group by fluorine [Table 2(*f*)] causes but little change.

Polyhalogeno-alkyl Iodides: $-CF_2\cdot CF_2I$, $I\cdot[CF_2]_n\cdot I$, $-CF_2\cdot CFClI$, CCl_3I, CBr_3I.—The spectra of a series of compounds containing the $-CF_2\cdot CF_2I$ group are shown in Table 3(*a*). Trifluoroiodomethane and pentafluoroiodoethane are too volatile for convenient spectral measurements in solution but the vapour spectra show a broad maximum at 268 mμ, *i.e.*, a bathochromic shift relative to methyl or ethyl iodide of 10 mμ. The spectrum of heptafluoroiodopropane is very similar when measured for the vapour or for the solution. The spectra of the series $CF_3\cdot[CF_2]_n\cdot I$ are closely similar when $n > 2$, although a slight shift to red is apparent as n changes through 0, 1, 2.

The bathochromic shift on changing from $CF_3\cdot CHF\cdot CF_2I$ to $CF_3\cdot CF_2\cdot CF_2I$ is only 2 mμ, and again shows that one or two atoms of hydrogen or fluorine can be interchanged on the β-carbon atom of the $CF_3\cdot C\cdot C\cdot I$ system without major influence on the spectrum.

The spectra of the perfluoro-alkyl di-iodides $I\cdot[CF_2]_n\cdot I$ with $n > 4$ [Table 3(*b*)] closely resemble those of the $CF_3\cdot[CF_2]_n\cdot I$ series and show that the chromophoric effects are additive and not transmitted by four or more CF_2 groups. When $n = 2$, however, appreciable interaction occurs, since there is a shift of the maximum to longer wavelength of 10 mμ, with substantial (*ca.* 50%) increase in intensity.

Examination of the series $CF_2X{\cdot}CF_2I$ [X = H, F, Cl, Br, Table 3(*a*); X = I, Table 3(*b*)] reveals the effect of auxochrome change on the β-carbon atom. The bathochromic shifts are given in Table 4 for vapour spectra, and the marked increase in intensity, particularly when X = I, is noteworthy.

TABLE 3.

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
(*a*) $-CF_2{\cdot}CF_2I$.				
CF_3I	267·5 *	155	—	—
C_2F_5I	268·5 *	165	224	105
n-C_3F_7I	271	240	215	13
	271 *	195	229	22
n-C_4F_9I	271	270	215	11
n-$C_5F_{11}I$	271	275	213	14
n-$C_6F_{13}I$	271	290	214	18
n-$C_7F_{15}I$	271·5	285	216	20
$CHF_2{\cdot}CF_2I$	266	255	215	14
	264 *	280	222	28
$CF_2Cl{\cdot}CF_2I$	272	295	215	17
	269 *	245	220	24
$CF_2Br{\cdot}CF_2I$	273	385	236	140
	269·5 *	343	237·5	125
(*d*) CX_3I.				
CCl_3I	324	—	—	—
CBr_3I	346	333	—	—

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
(*b*) $I{\cdot}[CF_2]_n{\cdot}I$.				
n				
2	282·5	1120	223	104
	280 *	—	228	—
4	272·5	690	220	95
6	272	670	219	55
8	272	690	220	65
(*c*) $-CF_2{\cdot}CFClI$.				
n in				
$CF_3{\cdot}[CF_2{\cdot}CFCl]_n{\cdot}I$				
1	286	300	229	28
2	291	345	234	35
3	292	375	244	120
4	292	340	243	100
5	292	390	242	145
$CF_2Cl{\cdot}CFClI$	283	315	229	26
$CF_2Br{\cdot}CFClI$	288	375	245	110

* For vapour spectra, otherwise light petroleum solutions.

TABLE 4.

X	H	F	Cl	Br	I
$\Delta\lambda$ (mμ)		4	1	10	

The large shift to the red (14 mμ) for $-CF_2{\cdot}CF_2I$ relative to $-CH_2{\cdot}CH_2I$ was noted above. A further large shift of 15 mμ is obtained by replacement of one α-fluorine atom by chlorine to give $-CF_2{\cdot}CFClI$ [Table 3(*c*)]. Further changes can be detected when a β-fluorine atom is replaced by chlorine or bromine (cf. $CF_2Cl{\cdot}CFClI$, $CF_2Br{\cdot}CFClI$). The effect of increase in chain length on absorption is shown by the series $CF_3{\cdot}[CF_2{\cdot}CFCl]_n{\cdot}I$: change from $n = 1$ to $n = 2$ gives a distinct shift to red of 5 mμ, but further increase in n has little effect; the absorption of the maximum merges with the general absorption of the $CF_2{\cdot}CFCl$ chain as n increases, until when $n > 6$—10, only an inflection can be observed.

The two polyhalogeno-alkyl iodides containing at least two α-halogen atoms other than fluorine so far studied are trichloro- and tribromo-iodomethane. Very large bathochromic shifts are observed: 53 and 75 mμ respectively relative to a perfluoroalkyl iodide such as trifluoroiodomethane and heptafluoroiodopropane, or 67 and 89 mμ relative to methyl or ethyl iodide.

The changes in wave-length on replacement of α- or β-hydrogen in $-\overset{\beta}{C}H_2{\cdot}\overset{\alpha}{C}H_2I$ are summarised in Table 5. These large changes are very valuable in determination of constitution of unknown polyhalogeno-organic iodides.

TABLE 5.

α-Substituents	HH	HH	HF	HH	FF	FF	HCl	HCl	FCl
β-Substituents	HH	FF	HH	FBr	HF	FF	HH	HF	FF
$\lambda_{max.}$	258	262	262	266	269	271	278	280	286

DISCUSSION

The ultra-violet absorption spectra of non-halogen-substituted organic iodo-compounds have been studied. Mulliken (*J. Chem. Phys.*, 1940, **8**, 382; *Phys. Review*, 1935, **47**, 413) suggested that the ultra-violet continua of the hydrogen and alkyl halides are $N \longrightarrow Q$ transitions. In hydrogen iodide or methyl iodide the long-wave-length continuum extends at least far enough to indicate that at least a small fraction of the

molecules dissociate to give a $^2P_{1\frac{1}{2}}$ iodine atom. Porret and Goodeve (*Proc. Roy. Soc.*, 1938, *A*, **165**, 31) concluded that for methyl iodide the *A* band leads to dissociation to give an excited $^2P_{\frac{1}{2}}$ iodine atom and a normal unexcited methyl free radical, whereas absorption of light in the *B* band gives products both of which are unexcited.

In considering the bathochromic shifts in the 250—350-mμ region outlined above, factors which may be involved are (*a*) the effect of the substituent halogen as an auxochrome, (*b*) the resonance stabilisation of a radical C–C· derived from C–Cl, and (*c*) steric effects. These factors will be considered separately although clearly all three play a part, and are inter-related.

(a) *Auxochromic Effect of Halogen.*—A chromophore is usually defined as a covalently unsaturated centre containing π-electrons, but for purposes of discussion the iodine atom will be regarded as a chromophore, and the substituents as auxochromes. Auxochromes produce increases in $\lambda_{max.}$ and in $\varepsilon_{max.}$, and are most effective when they are covalently unsaturated or contain unshared electron pairs.

The ultra-violet spectra of trichlorofluoromethane and dichlorodifluoromethane lie at shorter wave-length than those of chloroform or methylene chloride respectively, so that replacement of hydrogen by fluorine here causes a shift of absorption to the blue (Lacher, Hummell, Bohmfalk, and Park, *J. Amer. Chem. Soc.*, 1950, **72**, 5486). In substituted ethylenes, however, replacement of hydrogen by fluorine causes a shift to the red, presumably by increase in resonance, with structures such as $CHCl{:}CHF \longleftrightarrow \overset{-}{C}HCl{\cdot}CH{:}\overset{+}{F}$ increasing with the number of halogens attached directly to the double bond.

Consider now the halogen-substituted organic iodides. The contribution of non-classical resonance forms in a molecule is commonly considered to be greater in the excited than in the ground state; decrease in their energy content decreases the energy of the excited state more than that of the ground state, and this produces a shift to the red of the wave-length concerned with the electronic transition. In the undissociated molecule of the iodo-compound, direct interaction between the unshared electron pairs of iodine and a substituent X on the α-, β- or γ-carbon atom is possible [*e.g.*, $RCX_2{\cdot}CX_2I \longleftrightarrow X^-\ RC(\overset{+}{:}X){\cdot}CX(\overset{+}{:}I)\ X^-$], and hyperconjugation effects must also be considered (*e.g.*, $RCX_2{\cdot}CH_2I \longleftrightarrow X^-\ CRX{:}CHI\ H^+$; $CF_3{\cdot}CH_2{\cdot}CH_2I \longleftrightarrow F^-\ CF_2{:}CH{\cdot}CH_2I\ H^+ \longleftrightarrow F^-\ CF_2{:}\overset{H^+}{C}H{\cdot}\overset{H^+}{C}H{:}I^+$). If such effects played a *major* part in determining the very large shifts observed in the spectra, it would follow from the data that the auxochromic effect for a halogen, X, on the α-carbon atom increased in the order $X = H < F < Cl < Br < I$, *i.e.*, with descent of the Periodic Group, and increased availability of the lone pairs of X (cf. Ramart-Lucas and co-workers; references given by Braude, *J.*, 1949, 1902). The above effects are, however, considered to be less important than those discussed in (b) below.

Until relatively recently it was considered that the absorption due to chromophores separated by one or more CH_2 groups was additive, but there is increasing evidence that this is not completely valid (Ramart-Lucas *et al.*, *loc. cit.*; Braude, *loc. cit.*; Hillmer and Paersch, *Z. physikal. Chem.*, 1932, **161**, 46). Examination of the series $I{\cdot}[CF_2]_n{\cdot}I$ and $I{\cdot}[CH_2]_n{\cdot}I$ shows that interaction between the chromophores occurs when $n = 2$. The bathochromic shift is larger with the fluorine compound, and this can be attributed to the greater auxochromic effect of fluorine relative to hydrogen in the undissociated molecule, or to a difference in radical stability (see below).

(b) *Relative Stabilities of Radicals.*—If it is accepted that the absorption of light by the halogeno-alkyl iodide in the region of peak continuous absorption brings about dissociation of the molecule into a radical and an iodine atom $\cdot C{\cdot}C{\cdot}I \longrightarrow \cdot C{\cdot}C{\cdot} + \cdot I$, the change in position of absorption maximum can be correlated with the C–I bond dissociation energy, and with the relative stabilities of the ·C·C· radicals. It is suggested that the stability of the ·C·C· radical is the most important factor involved in determining the position of the absorption maximum; the more stable the radical, the further into the red will be the absorption maximum of its iodide.

In the alkyl iodides, RI, the bathochromic shifts run parallel to the ionisation potentials (I.P., ev) of the alkyl radical, the dissociation energy of the carbon–iodine bond, R–I

(kcal./mole), the resonance energies of the hydrocarbon radicals (R.E., kcal./mole, calculated and observed), and the stabilisation energies (S.E., kcal./mole) of the radicals relative to the methyl radical. These values are shown in Table 6 and are taken from papers by Baughan, M. G. Evans, and Polanyi, Baughan and Polanyi, Butler and Polanyi, Butler, Mandel, and Polanyi, and by A. G. Evans (*Trans. Faraday Soc.*, **1941**, **37**, 377; **1943**, **39**, 19; **1944**, **40**, 384; **1945**, **41**, 298; **1946**, **42**, 719); carbon–bromine and carbon–hydrogen bond dissociation energies are included.

TABLE 6.

	Me	Et	Pr^n	Pr^i	Bu^n	Bu^t	$CH_2{:}CH{\cdot}CH_2$
I.P.	13·60	10·07	8·67	7·77	—	7·19	—
R–I	54·0	52·0	50·0	46·5	49·0	45·0	39
R.E., calc.	0	7·05	8·6	14·1	—	21·1	—
obs.	0	7·2	8·1	12·6	—	16·7	—
S.E.	0	2	4	7·5	5	9	—
R–Br	68·5	67·0	64·5	61·0	63·5	60·0	—
R–H	102·5	97·5	95·0	89·0	94·0	86·0	—
$\lambda_{max.}$ (mμ)	257	258	258	261	—	270	271

Resonance stabilisation of alkyl radicals can occur by hyperconjugation [*e.g.*, $H{\cdot}CH_2{\cdot}\dot{C}Me_2 \longleftrightarrow H{\cdot}\ CH_2{:}CMe_2$], and in the *tert.*-butyl, *iso*propyl, and *n*-propyl radicals, for example, nine, six, and two C–H bonds respectively are available for this (Wheland, *J. Chem. Phys.*, 1934, **2**, 474). Radical stabilisation thus decreases in that order, and this is reflected in the spectra of the corresponding iodides. Resonance stabilisation of radicals substituted by halogen on the α- or β-carbon atom can be visualised *e.g.*:

$$\cdot CX_2{\cdot}\dot{C}X_2 \longleftrightarrow \cdot CX_2{:}\overset{+}{\dot{C}}X \qquad X^- \longleftrightarrow \cdot CX_2{\cdot}\ddot{C}X \quad \dot{X}$$

$$\cdot CX_2{\cdot}\dot{C}X{-}\ddot{\underset{\cdot\cdot}{X}}{:} \longleftrightarrow \cdot CX_2{\cdot}\bar{C}X{-}\overset{+}{\ddot{\underset{\cdot\cdot}{X}}}{:} \qquad\qquad \cdot CX_2{\cdot}\dot{C}X_2 \longleftrightarrow \dot{X} \quad \cdot CX{:}CX_2$$

The importance of β-halogen in stabilising the radical is shown by the series $CF_2X{\cdot}CF_2I$ (X = H, F, Cl, Br, I) considered above.

The greater chromophore interaction in $ICX_2{\cdot}CX_2I$ when X = F than when X = H can thus be explained, since the $I{\cdot}CF_2{\cdot}CF_2{\cdot}$ radical will be more stable than the $I{\cdot}CH_2{\cdot}CH_2{\cdot}$ radical. Similarly the marked difference in the spectra of methylene iodide and ethylene di-iodide can be ascribed to the greater stability of the $\cdot CH_2I$ compared with the $CH_2I{\cdot}CH_2{\cdot}$ radical. The slight shift to red in the spectra of the series CF_3I, C_2F_5I, C_3F_7I can also be attributed to increased radical stabilisation by the β- or γ-fluorine atoms.

For halogen substitution on the α-carbon atom, the shifts to red increase in the order H < F < Cl < I and with the number of α-halogen atoms. A sequence of decreasing radical stability is thus obtained, shown in Table 7, reading down each column and following-on in columns from left to right.

TABLE 7. *Radicals of type* $\geqslant C{\cdot}C{\cdot}$.

$CBr_3{\cdot}$	$CF_2Cl{\cdot}CFCl{\cdot}$	$CF_3{\cdot}[CF_2]_n{\cdot}$
$CCl_3{\cdot}$	$CF_2{\cdot}CHF{\cdot}CHCl{\cdot}$	$CF_2{\cdot}CHF{\cdot}CF_2{\cdot}$
$CF_3{\cdot}[CF_2{\cdot}CFCl]_{2\text{–}5}{\cdot}$	$CF_3{\cdot}CH_2{\cdot}CHCl{\cdot}$	$CHF_2{\cdot}CF_2{\cdot}$
$CF_2Br{\cdot}CFCl{\cdot}$	$CF_2Br{\cdot}CF_2{\cdot}$	$CF_3{\cdot}CH_2{\cdot}CHF{\cdot}$
$CF_3{\cdot}CF_2{\cdot}CFCl{\cdot}$	$CF_2Cl{\cdot}CF_2{\cdot}$	

Stabilisation by β- or γ-halogen is shown in the secondary radicals $CF_3{\cdot}CH_2{\cdot}\dot{C}HMe$ and $CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CH_2Cl$, $CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CF_3$, and $CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CF_2Cl$. Stabilisation of a secondary radical by CO_2Me is greater than that by a saturated alkyl or halogeno-alkyl group (cf. $CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me$ and $CF_3{\cdot}CH_2{\cdot}\dot{C}HMe$ etc.).

The sequence of decreasing stabilities for alkyl radicals substituted by halogen on the β- or γ-carbon atom is shown in Table 8.

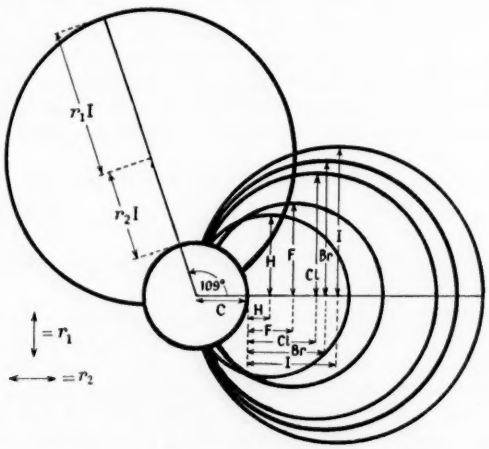
The correlation between absorption maximum and radical stability is, of course, only qualitative, and assumes that the differences in the vibrational energies of the radicals are not of major importance and that changes in the absorption maximum are due mainly to changes in the resonance energies of the radicals. The relative stabilities of radicals

estimated from the ultra-violet spectroscopic data run parallel, however, to the data on radical stability obtained from chemical evidence which is being presented in another series (Haszeldine, *J.*, 1952, 2504; Haszeldine and Steele, *Chem. and Ind.*, 1951, 684; *J.*, 1953, 1199 *et seq.*).

TABLE 8. *Relative radical stabilities when no halogen is present on the α-carbon atom.*

$\geqslant C\text{-}CH_2\cdot$	$(\geqslant C)_2CH\cdot$	$(\geqslant C)_3C\cdot$
$\cdot CH_2\cdot CO_2H$	$CF_3\cdot CH_2\cdot \dot{C}H\cdot CO_2Me$	$\cdot CMe_3$
$CH_2{:}CH\cdot CH_2\cdot$	$CF_3\cdot CH_2\cdot \dot{C}H\cdot CF_2Cl$	$\cdot CMe_2Et$
$CF_2Br\cdot CH_2\cdot$	$CF_3\cdot CH_2\cdot \dot{C}H\cdot CF_3$	
$CF_3\cdot CH_2\cdot$	$CF_3\cdot CH_2\cdot \dot{C}H\cdot CH_2Cl$	
$CF_3\cdot CH_2\cdot CH_2\cdot$	$\cdot CHMe_2$	
$CH_3\cdot [CH_2]_n\cdot$	$\cdot CHMeEt$	
	cyclo-$C_6H_{11}\cdot$	
	cyclo-$C_5H_9\cdot$	

In assessing the relative importance of the effects so far considered, the resonance effects in the *undissociated* molecule could often lead to an increase in carbon–iodine bond



	H	F	Cl	Br	I	C
van der Waals radii (r_1)	1·2	1·35	1·80	1·95	2·15	—
Covalent radii (r_2)	0·3	0·64	0·99	1·14	1·33	0·77

strength, and consequently could offset to some extent the decrease in bond strength caused by radical stability. That the effects on the undissociated molecule are of minor importance relatively to the stability of the radical R may be judged from the R–H dissociation energies (Table 6). The trend is the same as for the R–Br and R–I dissociation energies, yet only small resonance effects are to be expected in the C–H bond.

(c) *Steric Effects.*—In substitution of halogen for hydrogen on the α-carbon atom, steric effects might be expected to play a part as the halogen atom increases in size, since some stabilisation of the radicals given in Table 7 will occur by the change from the tetrahedral angle of $-CX_2$ in the $-CX_2I$ molecule to the (presumably) planar $-CX_2\cdot$ radical, by virtue of the steric interaction between X and I when X = Cl, Br, I (see below), which will be lost during dissociation, with consequent decrease of the repulsion energy. The interaction between X and I in a substituted alkyl iodide can be seen from the Figure, where the van der Waals and covalent radii have been taken from Pauling ("Nature of the Chemical Bond," Cornell Univ. Press, 1945). When X in $-CHXI$ is hydrogen or fluorine, only slight overlap occurs with the iodine atom, but when X = Cl, Br, or I, the steric interaction is appreciable. For $-CX_2I$ or CX_3I the steric effect would be increased further.

If the steric effect were of major importance it might be expected that it would be detectable in the carbon–iodine bond lengths. Although little is yet known about the

polyhalogeno-iodo-compounds discussed above, the carbon–iodine bond length in trifluoroiodomethane (2·16 Å; Sheridan and Gordy, *Phys. Review*, 1950, **77**, 292) is close to that in methyl iodide (2·13 Å), and since little variation is found in bond length in the series CH_3I, CH_2I_2 (2·12 Å), CHI_3 (2·12 Å) and CI_4 (2·12 Å) (Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46, give relevant references), it can be predicted that the carbon–iodine bond length will not vary greatly in compounds $-CX_2I$ (X = F, Cl, Br, I).

Butler, Mandel, and Polanyi (*loc. cit.*) noted a decrease in carbon–iodine bond strength when halogen is present on the α- or β-carbon atom. There is some doubt about the precise accuracy of these bond strengths: $CHCl_2I$, 42·4; $CHBr_2I$, 41·4; CHI_2–I, 37; $CH_2Cl{\cdot}CH_2I$, 45·9 kcal./mole (cf. alkyl iodides, Table 6), but the general trend is clear.

It is thus concluded that the resonance stabilisation of the radical is of greater importance and it can be predicted that the carbon–iodine bond dissociation energies of the compounds discussed in this paper will decrease in the orders given by radical stabilities shown in Tables 7 and 8.

Szwarc and Sehon (*J. Chem. Phys.*, 1951, **19**, 656) have shown by pyrolysis studies that the carbon–bromine bond dissociation energy decreases markedly in the several series, CH_3Br, CF_3Br; CH_2ClBr, $CHCl_2Br$, CCl_3Br; CH_2Br_2, $CHBr_3$, CBr_4, and point out that the available structural data do not reveal any significant change in carbon–bromine bond lengths. These facts, the decrease in bond dissociation energy on passing from CH_3–H to CCl_3–H (which can hardly be attributed to steric repulsion), the decrease in the carbon–carbon bond strength in chloral and bromal relative to acetaldehyde (Pritchard and Skinner, *J.*, 1950, 1928), and the difference in carbon–chlorine bond energies (10 kcal./mole) for methyl chloride and carbon tetrachloride, can also be correlated with the resonance stabilisation of the CX_3 radical.

The extent to which the assumptions made in the above correlations of radical stability and absorption spectra are justified will be seen only when further physical data (bond lengths and dissociation energies, ionisation potentials, etc.) are available. Until such a time the correlations give a means of estimating the relative stabilities of unknown free radicals, and their application in this connection will be described in another series.

Experimental

The alkyl iodides were commercial samples purified by distillation. The halogen-containing iodo-compounds were prepared in this laboratory by the author (*J.*, 1949, 2856 *et seq.*; *J.*, 1951, 584 *et seq.*; *J.*, 1952, 584 *et seq.*; *J.*, 1952, 4423), or by Mr. B. R. Steele (Haszeldine and Steele, *J.*, 1953, 1199), to whom due acknowledgment is made.

The spectra were usually determined in duplicate, maxima being read to 0·25 mμ, and average values are reported. Beckman DU and Unicam Spectrophotometers were used, with 1-, 4-, and 10-cm. silica cells for liquids and 4- and 10-cm. silica cells for vapours. The extinction coefficient (ε) for the vapour was calculated from $\varepsilon = 760 \times 22{\cdot}4 \times DT/273\,lp$ where D = optical density, T = temperature (K), l = cell length (cm.), and p = pressure of vapour (mm.), and is liable to appreciable error when pressures <10 mm. were required in a 4-cm. cell; pressures were read to ±0·5 mm.

The light petroleum had b. p. 60—80° and was purified by treatment with fuming sulphuric acid and alkaline permanganate, and showed 43% transmission at 210 mμ. Ethanol was obtained by drying 95% ethanol, and showed 42% transmission at 210 mμ.

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University Chemical Laboratory, Cambridge. [*Received, February 2nd*, 1953.]

364. *A New Reagent for the Titration of Water.*

By R. Belcher and T. S. West.

A new reagent for the determination of water in inert organic solvents is described. It consists of a solution of sulphur dioxide and bromine in chloroform, and it is used similarly to the conventional Karl Fischer reagent. Dioxan, benzene, pyridine, acetonitrile, and glacial acetic acid are less satisfactory than chloroform as solvent. The results obtained from the new reagent are more nearly stoicheiometric than those given by the Karl Fischer reagent, and it appears to be more stable. The change in redox potential at the end-point of the titration is very sharply defined, and a visual end-point depending on the disappearance of the colour of bromine from solution is as satisfactory as the potentiometric end-point. The reagent is cheaper than the Fischer reagent. Its main disadvantage is that alcohols interfere with the determination of water, but in most cases where a preliminary extraction of moisture is necessary, alcohol can be replaced by dioxan. The reaction products formed between pyridine, alcohol, and the reagent have been identified, and an acid–base method for the determination of water, based on these observations, has been suggested.

Many methods are available for the determination of water, but the only direct titrimetric method which has achieved wide usage is that of Karl Fischer (*Angew. Chem.*, 1935, **48**, 394) in which a solution of iodine, sulphur dioxide, and pyridine in methanol is used. The reaction of this reagent with water may be represented by $I_2 + SO_2 + H_2O \longrightarrow 2HI + SO_3$, but the freshly prepared reagent gives results of only approximately 80% of the theoretical value. After one month the proportion may drop to 50%, and in three months to 40%. This instability is the main drawback to the Fischer reagent.

We have examined some fifty reactions with a view to their development for the determination of water, but only one was found suitable, and this was based on the substitution of bromine for iodine in the Fischer reagent. Although this change had been suggested by Mitchell and Smith ("Aquametry," Interscience Publ., New York, 1948, p. 389) there is no record of its having been examined. The reaction is known to take place in aqueous medium according to the scheme $Br_2 + SO_2 + 2H_2O \longrightarrow H_2SO_4 + 2HBr$, and has been used to dry pyridine before distillation (Johansson, *Acta Chem. Scand.*, 1949, **3**, 1058).

Methanol could not be used as solvent because it reacted vigorously with the other constituents. A pyridine solution of bromine and sulphur dioxide was prepared, which reacted vigorously with all the lower aliphatic alcohols as well as with water. This reagent showed promise, but proved unsuitable: its water equivalence diminished gradually and, after storage overnight even in a dark cupboard, it had entirely lost its reactivity and a highly crystalline, dark brown precipitate had settled. After purification, a light brown compound, $C_{10}H_{10}N_2Br_2$ was obtained which contained bromine and nitrogen, but no sulphur. The crude product $C_{10}H_9N_2Br,H_2O$ decomposed without melting at *ca.* 300°.

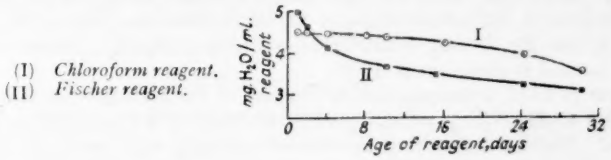
It was apparent from the instability of the reagent containing pyridine that any development of a direct method lay in the use of a solution of bromine and sulphur dioxide in an inert solvent such as benzene or chloroform, and the inclusion of the base in the solution of water to be titrated, rather than directly in the reagent solution as with the Karl Fischer reagent.

Anhydrous chloroform was found to be suitable for this purpose, for it dissolved bromine and sulphur dioxide to give a deep red solution which fumed in moist air, and was immediately decolorised on addition of excess of water in pyridine, with evolution of heat. Addition of anhydrous pyridine to the reagent solution caused an immediate diminution in the intensity of its red colour owing to formation of the addition compound between bromine and pyridine, but no further reaction was observed. On potentiometric titration of the reagent into a solution of water in pyridine, a steady potential was recorded after addition of the first few drops of titrant, and this was maintained till the end-point was reached, whereupon there was a sharp change in potential equivalent to 560 mv, and

simultaneous disappearance of the last trace of bromine colour afforded an excellent visual end-point. A reverse titration procedure was used (*i.e.*, the aqueous solution was run into a measured amount of reagent) because a better response was obtained from the polarised bi-platinum system. The spent reagent solution was water-white, and the products were completely soluble in the chloroform and pyridine, whereas, under the reverse conditions, precipitation of the reaction products occurred and a false end-point was sometimes obtained. Consequently, solutions of water of unknown concentration were analysed by careful addition to a measured excess of reagent, and back-titration of the excess with the standard solution of water in pyridine.

Stoicheiometry, and Stability of the Reagent.—The reaction between the reagent and a standard solution of water in pyridine was approximately 90% of that required by $Br_2 + SO_2 + H_2O \longrightarrow 2HBr + SO_3$, so the reaction taking place in the organic solvent may be analogous to that shown to take place in the Fischer reaction (Smith, Bryant, Mitchell, *J. Amer. Chem. Soc.*, 1939, **61**, 2407), *viz.*, $C_5H_5N,Br_2 + C_5H_5N,SO_2 + C_5H_5N + H_2O \longrightarrow 2C_5H_5N,HBr + C_5H_5N,SO_3$.

The new reagent therefore possesses the following advantages over the Fischer reagent. (i) It reacts more nearly quantitatively: 90% as compared with 80% for freshly prepared reagents. (ii) The change in potential at the end-point is more sharply defined. (iii) The visual end-point (red to water-white) is more easily observed than that (red-brown to pale brown) with Fischer's reagent. (iv) It has superior stability, as seen from the figure, which shows the change of water equivalence (mg. of water per ml. of reagent)



with time for both reagents. (v) It is probably more economical, bromine being cheaper than iodine, especially per equivalent.

A selection of results obtained by titration of a standard solution of water in pyridine against the reagent is given below.

Water taken, mg. ...	2·50	5·00	7·50	10·00	12·50	15·00	20·00	25·00	40·00
Water found, mg. ...	2·50	5·02	7·52	10·00	12·50	14·98	20·00	24·99	40·00

In determinations where an alcohol is normally used to extract moisture from the substance under analysis, it would be necessary to substitute dioxan before using the present reagent because of its reactivity towards alcohols. The extract could then be diluted with pyridine, and the analysis carried out on an aliquot of solution. The moisture content of organic solvents not containing hydroxyl groups could be determined similarly by dilution with pyridine and titration against the reagent.

Other Solvents.—A solution of water in pyridine being used for analysis, preparations of the reagent in various organic solvents not containing alcoholic or phenolic groups were examined. In benzene, the reagent solution was deep red and the reaction with the water solution was rapid, the visual end-point being coincident with an excellent potentiometric end-point. The reaction itself was satisfactory, proceeding to the extent of approximately 85—90%, but the insolubility of the products constituted a disadvantage.

Glacial acetic acid readily dissolved bromine and sulphur dioxide together, but titrations of water in pyridine could not be effected because of a reaction between the constituents of the solution on addition of anhydrous pyridine. Titrations of water in glacial acetic acid containing sodium acetate were possible, however, but the reagent solution decomposed more quickly than the chloroform reagent. Although of little use for general purposes, this reaction might be useful for the determination of moisture in acetic acid and its homologues.

Anhydrous dioxan readily dissolved sulphur dioxide and bromine, forming a light

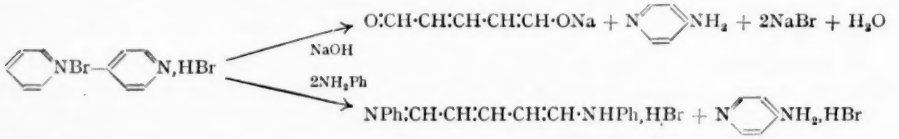
red solution which fumed in moist air. When this reagent was titrated with water in pyridine, two layers were formed: the lower layer appeared to contain most of the pyridine and practically all of the bromine and sulphur dioxide. Normally, dioxan and pyridine are miscible, and the presence of either bromine or sulphur dioxide alone does not cause separation of phases. When the polarised bi-platinum electrode system made contact with the upper layer only, no end-point could be detected potentiometrically until some considerable time after the lower red layer had been decolorised but, when the electrode system penetrated to the lower layer, reproducible electrometric end-points coincident with the visual end-points were obtained. The titration proceeded smoothly and rapidly with a sharp change in potential at the end-point, but the formation of insoluble products was an undesirable feature. The reaction was approximately 90% of the stoicheiometric value.

Anhydrous acetonitrile was the only solvent apart from chloroform which retained the reaction products in solution. The acetonitrile reagent was dark red, and its reaction with water in pyridine was rapid, both visual and potentiometric end-points being excellent and coincident. The spent reagent solution was colourless. Unlike the chloroform reagent, however, this solution of bromine and sulphur dioxide decomposed entirely after a few weeks, forming a black deposit.

All attempts to prepare a composite reagent containing bases other than pyridine (quinoline, quinaldine, aniline, piperidine, and morpholine) failed, the base reacting with the other constituents.

Reaction of the Reagent with Alcohols and Pyridine.—Reaction of the reagent with alcohols might yield a dialkyl sulphate or an alkyl bromide: $Br_2 + SO_2 + 2R{\cdot}OH \longrightarrow 2HBr + R_2SO_4$ or $Br_2 + SO_2 + 2R{\cdot}OH \longrightarrow 2RBr + H_2SO_4$. Proof that the alkyl sulphate was formed is given on p. 1776.

As stated on p. 1772, a decomposition product of the pyridine-containing solution had the composition $C_{10}H_{10}N_2Br_2$, which agrees with that of 4-1′-pyridylpyridinium bromide hydrobromide. The corresponding dichloro-compound was prepared by Koenigs and Greiner (*Ber.*, 1931, **64**, 1045, 1049) by reaction of thionyl chloride and pyridine. Our bromo-compound showed the behaviour characteristic of this type of compound, *viz.*, cleavage of the pyridine ring by cold dilute aqueous alkali to form the intensely yellow derivative of glutaconic dialdehyde. Furthermore, on reaction with aniline under reflux in alcohol, it afforded glutaconanil hydrobromide (anil–anilino-form):



This compound was prepared by Zincke (*Annalen*, 1904, **333**, 317) by a different route. Qualitative tests using α-naphthylamine in place of aniline gave a bright scarlet precipitate, and 4-1′-pyridylpyridinium hydrochloride reacted in identical manner.

This behaviour of the reagent with pyridine and aliphatic alcohols parallels that of sulphuryl chloride with these substances and suggests that a mixture of bromine and sulphur dioxide behaves in certain respects as sulphuryl bromide would be expected to react. Sulphuryl bromide has never been isolated, but might exist to a slight extent in equilibrium in the reagent solution. Sulphuryl iodide would be well nigh incapable of existence in even equilibrium amounts and this sequence of stability may explain why the bromine reagent reacts with alcohols while the conventional Fischer reagent does not.

Acid–Base Method for Determination of Water.—Although water liberates 4 equivs. of acid per molecule of reagent (the SO_3 behaves as a dibasic acid on addition of water), alcohols liberate only two. We have applied this reaction in developing an alternative, simple alkalimetric method using a common acid–base indicator. An excess of reagent was allowed to react with the solution of water in pyridine, and the excess was destroyed by addition of an excess of anhydrous alcohol. The acid thus formed was titrated with

standard alkali, and from this titre was deducted the titre obtained from reaction of an identical amount of reagent with excess of anhydrous alcohol. The net titres thus obtained were strictly proportional to the weights of water taken.

The reagent solution used for this determination contained an excess of bromine, since it was difficult to titrate accurately the weak sulphurous acid formed by the excess of sulphur dioxide present in the former reagent solution. The excess of bromine then remaining in the solution was destroyed by addition of phenol before titration.

The method is advantageous in that only simple apparatus is required and that titration follows conventional lines; its drawbacks are the necessity to prepare anhydrous alcohol to react with the reagent, and the fact that the titre for water is obtained as a small difference between two relatively big titres. This is due to the stoicheiometry of the reactions, for the excess of reagent produced 4 equivs. of acid per mole of bromine in reaction with water, whereas the blank produced 2 equivs. of acid per mole of bromine on reaction with alcohol. Since a two-fold amount of reagent was used, the equivalence of one mole of water was found as the difference between (4 + 2) and 4 equivs. of acid.

Other Reactions investigated.—The following reaction is cited as an example of others that we examined for suitability for the determination of water. Cupric salts are reduced by aqueous sulphur dioxide as follows: $2CuCl_2 + SO_2 + 2H_2O \longrightarrow Cu_2Cl_2 + 2HCl + H_2SO_4$. A reagent prepared to contain anhydrous cupric chloride and an excess of sulphur dioxide in certain proportions of anhydrous methanol and pyridine reacted quite rapidly with a solution of water in methanol. Although reaction was slower than that with the Karl Fischer reagent under similar conditions, excellent end-points were obtained both visually and potentiometrically and titrations were reproducible. The speed of reaction with water decreased as the reagent solution aged, however, and after 5 days it was useless.

Experimental

Preparation of Reagent.—In chloroform dried by redistillation from phosphoric oxide, pure bromine was dissolved (15 ml. in 750 ml.) and the tightly stoppered container was chilled in ice–salt. Liquid sulphur dioxide (20 ml.) was added rapidly, with gentle shaking, and the volume of the solution adjusted to approx. 1 l. with anhydrous chloroform; 1 ml. of this solution was equivalent to approx. 5 mg. of water.

The water solution was prepared by dissolving 5 g. in 1 l. of anhydrous pyridine (prepared by distillation of pure reagent from phosphoric oxide). The equivalence of this solution was checked in the normal way by titration with a solution of Karl Fischer reagent which had been standardised against sodium acetate trihydrate

Titration Procedure.—The reagent and the water solution were placed in the reservoirs of a conventional Fischer-type apparatus. A Mullard " magic-eye " potentiometer unit was used to record the end-point of the titration in conjunction with an electrode system of two stout platinum wires led into the titration vessel through a ground-glass stoppered side arm. Stirring of the solution was effected by dry nitrogen. An appropriate amount of reagent solution was slowly delivered into the titration vessel from the burette mounted on the reagent reservoir, and the potentiometer system was connected to the mains supply with the switch in the polarising position. A few drops of the water solution were added slowly, and the solution gently stirred. Over-rapid addition of reagent to the titration vessel or of pyridine solution to the reagent caused loss of bromine by volatilisation due to the heat of reaction; once sufficient pyridine is present, however, there is no danger of loss of bromine in this way. The potentiometer unit recorded a steady potential as more water solution was added, and the colour slowly faded to pale yellow. The titration was finished dropwise, the solution being thoroughly stirred with dry nitrogen after the addition of each drop. At the end-point, the " eye " of the potentiometer unit closed sharply and could only be opened by applying a balancing voltage of some 560 mv. Simultaneously the last trace of yellow colour disappeared, leaving a transparent, colourless solution.

Reaction Products formed with Ethanol and with Pyridine.—Isolation of ethyl sulphate. Equivalent amounts of bromine and sulphur dioxide were added to anhydrous ethanol. A slight excess of sulphur dioxide was added if necessary to discharge the colour of bromine from the solution, and the excess of sulphur dioxide and alcohol was removed at a low temperature under reduced pressure. When water was added to the residual liquid, a pale yellow, oily layer separated, which was washed several times with dilute alkali and distilled water, dried

(Na_2SO_4), and distilled *in vacuo*. The purified liquid had the characteristic odour of ethy sulphate; b. p. 208° (decomp.) [Found : C, 31·1; H, 6·6; S, 20·6. Calc. for $(C_2H_5)_2SO_4$: C, 31·2; H, 6·5; S, 20·8%].

Isolation of 4-1′-*pyridylpyridinium bromide hydrobromide*. This substance was obtained from a reagent solution of 15 ml. of bromine and 20 ml. of sulphur dioxide in 1 l. of pyridine as a dark brown, crystalline deposit after the solution had been kept overnight. These crystals were insoluble in all the common solvents except alcohol and water, in which they were extremely soluble. Recrystallisation from alcoholic hydrobromic acid (charcoal) afforded pale brown needles, m. p. 160° (decomp.) (Found : C, 37·8; H, 3·1; N, 8·7; Br, 50·4. $C_{10}H_{10}N_2Br_2$ requires C, 37·8; H, 3·2; N, 8·8; Br, 50·3%). When an alcoholic solution of equivalent amounts of the above *compound* and aniline were refluxed for ½ hr., an intensely red solution was obtained which deposited red crystals on cooling. Recrystallised from alcohol several times, these had m. p. 168°. Zincke (*loc. cit.*) gave m. p. 167° (Found : C, 62·1; H, 5·1; N, 8·4; Br, 24·3. Calc. for $C_{17}H_{17}N_2Br$: C, 62·0; H, 5·2; N, 8·5; Br, 24·3%).

Acid–Base Method for Determination of Water.—The reagent used for this determination was prepared as described previously except that the quantities of bromine and sulphur dioxide were 28 and 16 ml., respectively, per l. Ethanol was rendered anhydrous by distillation from calcium. A measured excess of the reagent was delivered into a dry iodine flask and a few ml. of the solution of water in pyridine were carefully added. The flask was stoppered, and the contents gently mixed; after 1 min. anhydrous ethanol (1—2 ml.) was added, and the mixture vigorously shaken till the fumes in the flask had redissolved. The solution was then freed from bromine by addition of a few crystals of phenol, and the total acidity was found by titration with a solution of sodium ethoxide in ethyl alcohol, with phenolphthalein as indicator. (Under these conditions, the added phenol showed no acidity and could not be titrated either thus or by use of a pH meter.) The blank value was found by titration of an identical amount of reagent treated similarly, but without addition of the water solution. The difference in the two titres gave the titre equivalent to the amount of water reacting.

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365. *Diisopropyl Phosphorofluoridate.*

By A. H. FORD-MOORE, L. J. LERMIT, and C. STRATFORD.

Methods for preparing di*iso*propyl phosphorofluoridate from three different starting materials are described. Two are modifications of known methods and all give a product of high purity in yields of at least 60%. Some physical constants of material fractionated to constant refractive index are recorded.

DI*iso*PROPYL PHOSPHOROFLUORIDATE, $(Pr^iO)_2POF$, has been studied by McCombie, Saunders, and Stacey, and their co-workers (*J.*, 1945, 381; 1948, 698; *Nature*, 1946, **157**, 287). Their method of preparation was based on the steps :

$$(i)\quad 3Pr^iOH + PCl_3 \longrightarrow \underset{(I)}{HPO(OPr^i)_2} + Pr^iCl + 2HCl$$

$$(ii)\quad (I) + Cl_2 \longrightarrow \underset{(II)}{(Pr^iO)_2POCl} + HCl$$

$$(iii)\quad (II) + NaF \longrightarrow \underset{(III)}{(Pr^iO)_2POF} + NaCl$$

The phosphorochloridate (II) could also be obtained by the action of chlorine on tri*iso*propyl phosphite (cf. McCombie, Saunders, and Stacey, *loc. cit.*, 1945; Ford-Moore and Howarth Williams, *J.*, 1947, 1465; Ford-Moore and Perry, *Org. Synth.*, 1951, **31**, 111).

Saunders and Stacey (*loc. cit.*, 1948) also described a one-stage synthesis of (III) from *iso*propanol and phosphorus trichloride, neither (I) nor (II) being isolated, but the

present authors found difficulty in repeating this work. Certain modifications have therefore been introduced. Thus sulphuryl chloride (cf. Atherton, Howard, and Todd, *J.*, 1948, 1106) was found to react more smoothly than chlorine in stage (ii). In stage (iii), the use of ammonium fluoride (U.S.P. 2,409,039) was found more convenient than that of sodium fluoride.

When tri*iso*propyl phosphite was used as the starting material, carbonyl chloride was found to be a convenient reagent for its conversion into (II), apparently functioning as follows:

$$(Pr^iO)_3P + COCl_2 \longrightarrow \left[(Pr^iO)_3P\begin{matrix}COCl\\Cl\end{matrix}\right] \longrightarrow CO + Pr^iCl + (II)$$

This reaction proceeded equally well with primary alkyl phosphites such as triethyl phosphite. If desired, the pure phosphorochloridate could be isolated, by distillation, in about 90% yield. For conversion into (III), the crude (II), after removal of volatile matter under reduced pressure, was heated with dry ammonium fluoride in the absence of a diluent and the phosphorofluoridate isolated by vacuum distillation without filtration from the ammonium salts.

The simplest one-stage process is expressed by:

$$POCl_3 + 2Pr^iOH + 5NaF \longrightarrow (III) + 3NaCl + 2NaHF_2$$

An attempt to realise this reaction showed that it was uncontrollable, probably owing to decomposition of the intermediate *iso*propyl phosphorodichloridate (IV). But if the preparation of (IV) (though not the actual isolation, since it begins to decompose about 55°) was carried out as a separate stage, a good yield of (III) could be obtained:

$$Pr^iOH + POCl_3 \longrightarrow HCl + Pr^iO{\cdot}POCl_2 \quad (IV)$$

$$(IV) + Pr^iOH + 3NaF \longrightarrow (III) + 2NaCl + NaHF_2$$

Use of sodium fluoride in the final stage was quite satisfactory.

The phosphorofluoridate could also be obtained by treating (I) with sulphuryl chloride in the presence of sodium fluoride:

$$(I) + SO_2Cl_2 + 3NaF \longrightarrow (III) + 2NaCl + NaHF_2$$

Very pure phosphorofluoridate was obtained by fractional distillation under reduced pressure of good-grade material prepared as described above.

Experimental

Di*iso*propyl hydrogen phosphite was made by the method of McCombie, Saunders, and Stacey (*loc. cit.*). For certain of the preparations described, it was isolated and purified by distillation under reduced pressure. In others, *e.g.*, treatment with sulphuryl chloride, it was sufficient to remove hydrogen chloride and diluent by distillation and use the crude material. Triethyl and tri*iso*propyl phosphite were made by Ford-Moore and Perry's method (*loc. cit.*).

Diisopropyl Phosphorochloridate (II).—(*a*) Crude di*iso*propyl hydrogen phosphite, diluted with carbon tetrachloride, was treated with one equivalent of sulphuryl chloride (cf. Todd *et al.*, *loc. cit.*). The product, isolated by distillation under reduced pressure, had b. p. 68°/2 mm. (yield, 85—90%).

(*b*) Redistilled tri*iso*propyl phosphite (104 g.) was treated with a fairly rapid stream of carbonyl chloride, with stirring, the temperature being kept at 30—35°. Reaction was complete in about 1 hr., when rise of temperature and effervescence ceased. Next morning, the product was degassed at the water-pump and then distilled under reduced pressure, giving the phosphorochloridate (92 g., 92%), b. p. 63°/1 mm., n_D^{25} 1·4142 (Found: Cl, 17·9. Calc. for $C_6H_{14}O_3ClP$: Cl, 17·7%).

Diethyl phosphorochloridate (81 g., 94%), prepared from triethyl phosphite by a similar procedure on a 0·5-molar scale, had b. p. 54°/1 mm., n_D^{25} 1·4147 (Found: Cl, 20·6%).

Diisopropyl Phosphorofluoridate.—(*a*) Redistilled phosphorochloridate (100 g.) in dry acetone (200 c.c.) was treated with coarsely ground ammonium fluoride, previously dried by distillation with carbon tetrachloride. A mildly exothermic reaction set in; this was completed by 1 hr.' refluxing. After cooling, the mixture was filtered and the filter cake washed with dry

acetone. Removal of the diluent from the filtrate and distillation under reduced pressure gave crude fluoridate (82 g., 89%), b. p. 53°/4 mm., n_D^{25} 1·3791. When crude phosphorochloridate (from di*iso*propyl hydrogen phosphite and sulphuryl chloride) was used, the initial reaction was much more vigorous and external cooling was necessary. The yield of distilled product in a 0·5-molar run was 75 g. (81%, calc. on the crude ester).

(*b*) Di*iso*propyl phosphorochloridate (44·7 g., 41 c.c.) and dried ammonium fluoride (12 g.) were heated under reflux in an oil-bath. A vigorous reaction set in at about 120° (bath-temp.). When it had ceased, the mixture was cooled and filtered, the filter cake being washed with a little methylene chloride. The product (27 g., 71%), isolated by distillation under reduced pressure, had b. p. 52—53°/4 mm., n_D^{25} 1·3790.

One-stage Methods.—(*a*) A mixture of undistilled di*iso*propyl hydrogen phosphite (83 g., 0·5 mole) and dry sodium fluoride (75 g., 1·75 mole) in dry benzene was stirred under reflux and warmed to 35°. Sulphuryl chloride (42 c.c., 0·52 mole) was added, with cooling, at such a rate that the temperature was kept at 45—50°. After the addition, the mixture was stirred and refluxed for 2 hr. After cooling, dry kieselguhr (15 g.) was added and the mixture filtered, the filter cake being washed with dry benzene. Removal of solvent from the filtrate and distillation under reduced pressure gave di*iso*propyl phosphorofluoridate (63 g., 68%), b. p. 48°/3 mm., n_D^{25} 1·3794. Addition of the phosphite to the other reactants resulted in a lower yield.

(*b*) Dry *iso*propanol (38 c.c., 0·5 mole) was added slowly to phosphorus oxychloride (46 c.c., 0·5 mole) and carbon tetrachloride (100 c.c.) at 30—35°. The reaction was only mildly exothermic and little cooling was necessary. Next morning the diluent and hydrogen chloride were removed under reduced pressure, at ≯50°. A mixture of *iso*propanol (42 c.c., 0·55 mole) and sodium fluoride (75 g., 1·75 mole) in dry benzene or carbon tetrachloride was stirred and warmed to 40° (the lowest temperature for reaction). The crude *iso*propyl phosphorodichloridate was added at such a rate that the temperature was 45—50°. The mixture was then refluxed with stirring for 0·5 hr. and the phosphorofluoridate isolated as above (yield, 55 g.; b. p. 49°/3 mm., n_D^{25} 1·3790).

(*c*) Tri*iso*propyl phosphite (104 g., 0·5 mole) was stirred and treated at 30—35° (cooling) with a fairly rapid stream of carbonyl chloride. Next morning the mixture was degassed at the water pump till the pressure fell below 20 mm. and treated under a reflux fractionating column with dry ammonium fluoride (30 g., 0·75 mole) and then heated rapidly to 120° (oil-bath). When the vigorous reaction had moderated, the material was kept at 120° for a further 0·5 hr. The product (59 g.), isolated by distillation under reduced pressure, without filtering, had b. p. 46—47°/2·5 mm., n_D^{25} 1·3792. It was slightly turbid owing to a small amount of ammonium salts which could be removed by decantation after 2 days.

Pure Diisopropyl Phosphorofluoridate.—The various samples of high-grade material prepared as described above were combined and distilled under reduced pressure from about 5% (vol.) of diethylaniline, under a 15″ helix-packed column surmounted with a Whitmore–Lux total-reflux variable-take-off still-head, until the refractive index of the distillate, determined with an Abbé refractometer, was constant. It was collected at 41—42°/1·5 mm. (Found: C, 39·0; H, 7·8; F, 10·4. Calc. for $C_6H_{14}O_3FP$: C, 39·1; H, 7·7; F, 10·3%). The product had b. p. 42—43°/2 mm., d_4^{25} 1·0571, η 0·01323 poise, and n and v. p. as tabulated.

Temp.	10°	15°	20°	25°	30°
n_D	1·3854	1·3834	1·3814	1·3791	1·3773
V. p. (mm.)	—	0·48	0·72	1·08	1·61

This paper is published by permission of the Chief Scientist, Ministry of Supply, whom authors thank. Microanalyses were by F. E. Charlton and Miss B. A. Jones, vapour-pressure determinations by E. Neale, using an effusion manometer, and densities and viscosity by A. W. H. Wardrop.

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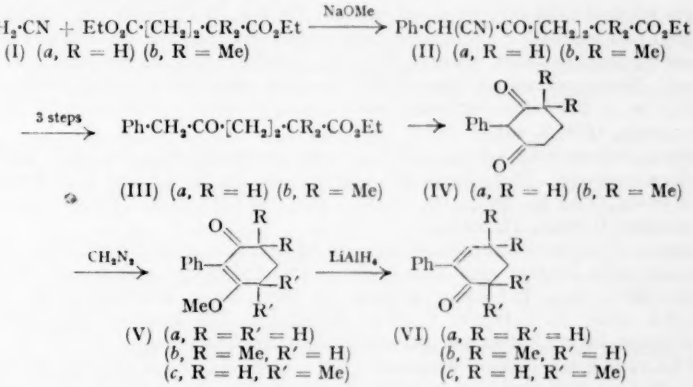
366. *Synthesis of* cyclo*Hexenones.*

By Harry Born, Raphael Pappo, and Jacob Szmuszkovicz.

Reduction of *cyclo*hexane-1 : 3-diones with lithium aluminum hydride opens a satisfactory route to the series of *cyclo*hex-2-enones. The reaction has been utilized for the preparation of a number of intermediates of current interest.

When enol ethers of *cyclo*hexane-1 : 3-diones are reduced with lithium aluminum hydride and the reaction products decomposed under acidic conditions, *cyclo*hex-2-enones are obtained. Frank and Hall (*J. Amer. Chem. Soc.*, 1950, **72**, 1645) thus prepared 5 : 5-dimethyl- and 5-*iso*propyl-*cyclo*hex-2-enone from the enol ethyl ethers and Blanchard and Goering (*ibid.*, 1951, **73**, 5863) synthesized 5-methyl*cyclo*hex-2-enone. Seifert and Schinz (*Helv. Chim. Acta*, 1951, **34**, 728) obtained aldehydes from alkyl ethers of hydroxymethylene-*cyclo*hexanone or -*cyclo*pentanone.

We find that the enol methyl ether of *cyclo*hexane-1 : 3-dione gives, on successive reduction and acid treatment, *cyclo*hex-2-enone in 85% yield overall from the diketone, which compares very favourably with that of the methods previously reported (Paquot, *Bull. Soc. chim.*, 1941, **8**, 695; Birch, *J.*, 1944, 430; Oppenauer and Oberrauch, *Anal. Asoc. Quim. Argentina*, 1949, **37**, 246; for other references, see Bartlett and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933). Analogously, 2-methyl*cyclo*hexane-1 : 3-dione was converted into 2-methyl*cyclo*hex-2-enone (Butz, Davis, and Gaddis, *J. Org. Chem.*, 1947, **12**, 122) in 95% yield, and the corresponding 2-phenyl compound (VI*a*) (Ginsburg and Pappo, *J.*, 1951, 516) was obtained in 45% yield.


Ph·CH₂·CN + EtO₂C·[CH₂]₂·CR₂·CO₂Et
NaOMe
Ph·CH(CN)·CO·[CH₂]₂·CR₂·CO₂Et
(I) (a, R = H) (b, R = Me)
(II) (a, R = H) (b, R = Me)
3 steps
Ph·CH₂·CO·[CH₂]₂·CR₂·CO₂Et
(III) (a, R = H) (b, R = Me)
(IV) (a, R = H) (b, R = Me)
CH₂N₂
LiAlH₄
(V) (a, R = R′ = H)
(b, R = Me, R′ = H)
(c, R = H, R′ = Me)
(VI) (a, R = R′ = H)
(b, R = Me, R′ = H)
(c, R = H, R′ = Me)

The diketone (IV*a*) was synthesized as follows. Benzyl cyanide was condensed with ethyl glutarate (I*a*) in the presence of sodium methoxide to give ethyl 6-cyano-5-keto-6-phenylhexanoate (II*a*). Hydrolysis, decarboxylation, and re-esterification afforded ethyl 5-keto-6-phenylhexanoate (III*a*), cyclized by sodium ethoxide or sodium hydride in ether to (IV*a*). The diketone with diazomethane afforded 3-methoxy-2-phenyl*cyclo*hex-2-enone (V*a*), whilst ethyl orthoformate gave the corresponding ethyl ether.

Employing benzyl cyanide and αα-dimethylglutarate (I*b*) gave 6 : 6-dimethyl-2-phenyl-*cyclo*hexane-1 : 3-dione (IV*b*) *via* (III*b*). The intermediates (II*b*) and (III*b*) might have the isomeric structures that would arise if the condensation with benzyl cyanide were to involve the quaternary ester group. The structures (II*b*) and (III*b*) appear, however, to be preferable on steric grounds, but no attempt has been made to elucidate this point, as the formula of the cyclization product (IV*b*) is the same for both reaction mechanisms. Reaction of (IV*b*) with diazomethane gave a mixture of 3-methoxy-6 : 6- (V*b*) ($\lambda_{max.}$ 268 mμ; *E* 13,700) and 3-methoxy-4 : 4-dimethyl-2-phenyl*cyclo*hex-2-enone (V*c*) ($\lambda_{max.}$ 263 mμ; *E* 12,000). (V*c*) is hydrolyzed more slowly than (V*b*) by boiling 5% aqueous sodium

hydroxide (Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828) and also shows a hypsochromic shift in the ultra-violet spectrum.

Reduction of (V*b*) with lithium aluminum hydride gave **4**:4-dimethyl-2-phenyl*cyclo*hex-2-enone (VI*b*) as an oil which was characterized as the red dinitrophenylhydrazone ($\lambda_{max.}$ 380 mμ; *E* 63,000), and reduction of (V*c*) gave **6**:6-dimethyl-2-phenyl*cyclo*hex-2-enone (VI*c*) which afforded an orange dinitrophenylhydrazone ($\lambda_{max.}$ 375 mμ; *E* 67,000). As expected, (VI*c*) shows a hypsochromic shift in the ultra-violet spectrum (cf. the spectrum of the dinitrophenylhydrazone of 2-phenyl*cyclo*hex-2-enone for which Ginsburg and Pappo, *loc. cit.*, reported $\lambda_{max.}$ 380 mμ; *E* 25,800).

Experimental

Ultra-violet spectra were determined by Dr. S. Pinchas and Mr. Ch. Eger using a Beckman spectrophotometer, model DU. Ethanol was the solvent.

cyclo*Hex*-2-*enone*.—Dihydroresorcinol (15 g.) (*Org. Synth.*, **27**, 21) was added to an excess of ethereal diazomethane. The solution was evaporated; the residue afforded on distillation a colourless oil (15·4 g.), b. p. 73°/0·5 mm., m. p. 37° (Found: C, 66·8; H, 8·1. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 8·0%).

Hydrolysis with N-hydrochloric acid at 60° for 1 hr. reversed the reaction and gave dihydroresorcinol.

The reduction with lithium aluminum hydride, carried out as usual, gave a 93% yield of material, b. p. 70°/26 mm. ($\lambda_{max.}$ 225 mμ; *E* 11,270). The dinitrophenylhydrazone melted at 167° (Bartlett, *loc. cit.*; Dimroth and Resin, *Ber.*, 1942, **75**, 322; Dimroth and Stockstrom, *Ber.*, 1942, **75**, 326) after one recrystallization from ethanol.

2-*Methyl*cyclo*hex*-2-*enone*.—Methylation of dihydroresorcinol (cf. Desai, *J.*, 1932, 1079; Frank and Hall, *loc. cit.*; cf. Bastron, Davis, and Butz, *J. Org. Chem.*, 1943, **8**, 515, footnote 2) has not been described in detail before. A solution of dihydroresorcinol (90 g., 0·798 mole) in absolute ethanol (453 ml.) to which sodium (21·6 g., 0·93 mole) was added was cooled in ice. Methyl iodide (161·7 g., 1·14 mole) was added and the mixture refluxed for 3·5 hr. The solvent was removed *in vacuo*, water (1·6 l.) added to the remaining red solid, and the precipitate filtered off. Recrystallization from water (norite) afforded 2-methyl*cyclo*hexane-1:3-dione (43 g. 43%), m. p. 210° alone or mixed with a sample prepared according to Blaise and Maire (*Bull. Soc. chim.*, 1908, **3**, 421).

2-Methyl*cyclo*hexane-1:3-dione (12·5 g.) was converted into the enol methyl ether with ethereal diazomethane. Distillation and recrystallization from water gave 3-*methoxy*-2-*methyl*-cyclo*hex*-2-*enone* (13·5 g., 96%), m. p. 46°, b. p. 90°/0·8 mm. (Found: C, 68·2; H, 8·8. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%).

Hydrolysis of the enol ether with 0·5N-hydrochloric acid gave 2-methyldihydroresorcinol.

Reduction with lithium aluminum hydride afforded 2-methyl*cyclo*hex-2-enone, b. p. 74—75°/25 mm. (99%) ($\lambda_{max.}$ 234·5 mμ; *E* 9850) (cf. Butz, Davis, and Gaddis, *loc. cit.*) (Found: C, 76·4; H, 9·5. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·2%). The dinitrophenylhydrazone melted at 207—208° (*idem*, *loc. cit.*) after one recrystallization from methanol.

Ethyl 6-*Cyano*-5-*keto*-6-*phenylhexanoate* (II*a*).—Benzyl cyanide (11·7 g., 0·1 mole) and ethyl glutarate (28·2 g., 0·15 mole) were added to a solution of sodium (3 g.) in absolute ethanol (35 ml.) with vigorous shaking, then heated on the steam-bath for 2 hr. with frequent shaking, and left at room temperature overnight. The sodium salt of (II*a*) usually crystallized at the end of this period and could be worked up in two ways: (*a*) The sodium salt was filtered off and washed as described in *Org. Synth.*, Coll. Vol. II, John Wiley, New York, 1943, p. 487. Acidification of its aqueous solution with acetic acid gave an oil which crystallized slowly when cooled and scratched. It was recrystallized from aqueous ethanol, m. p. 65° (sinters at 55°), and proved to be the *hydrate* of (II*a*) (Found: C, 64·9; H, 6·9. $C_{15}H_{17}O_3N,H_2O$ requires C, 65·0; H, 6·8%). The mother-liquor from the sodium salt, worked up as described (*op. cit.*), afforded an additional amount of crude sodium salt.

(*b*) When larger quantities were used the reaction mixture was acidified with a slight excess of acetic acid and then diluted with water. The whole was thoroughly extracted with ether, and the extracts were washed twice with water, dried ($MgSO_4$), and evaporated. Distillation afforded a fraction, b. p. 80—90°/1 mm. (starting materials), and (II*a*), b. p. 180—200°/1 mm. (66%; 80% based on the starting materials used). When (II*a*) was boiled for a short time with water the corresponding hydrate was obtained, m. p. 65°.

5-*Keto*-6-*phenylhexanoic Acid*.—A mixture of (II*a*) (50 g.), acetic acid (330 ml.), concentrated

hydrochloric acid (110 ml.), and water (100 ml.) was refluxed for 15 hr. in an atmosphere of nitrogen. The solvents were evaporated *in vacuo* and the residue was taken up in ether, washed twice with water, and extracted with aqueous potassium carbonate solution (5%). The alkaline layer was separated, washed once with ether, and acidified with dilute hydrochloric acid. An oil was obtained which crystallized after a short time. Extraction with ether and concentration gave *5-keto-6-phenylhexanoic acid* as an oil which crystallized. Recrystallization from di*iso*propyl ether gave long needles, m. p. 265° (Found : C, 69·8; H, 7·2. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%).

By azeotropic distillation with absolute ethanol (50 ml.), anhydrous benzene (100 ml.), and toluene-*p*-sulphonic acid (1 g.), the keto-acid (20 g.) gave the *ethyl* ester (20·4 g.), b. p. 140—160°/1 mm., m. p. 43—45°. Recrystallization (needles from hexane) (Found : C, 72·2; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

2-*Phenyl*cyclo*hexane*-1 : 3-*dione* (IV*a*).—(*a*) Sodium ethoxide in absolute ethanol proved unsatisfactory for the cyclization of (III*a*). The ester (III*a*) was therefore refluxed under nitrogen with two equivs. of alcohol-free sodium ethoxide in ether. A gum was precipitated immediately which became crystalline after 30 min. The mixture was refluxed for 1 more hr., cooled, acidified with dilute hydrochloric acid, and diluted with ether, and the ethereal solution was washed once with a little water. Upon evaporation of the solvent, the *diketone* (IV*a*) was obtained crystalline. Recrystallization from benzene gave plates, m. p. 160—161° (Found : C, 76·8; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). The dione (IV*a*) gives a violet colour with aqueous, but not with alcoholic, ferric chloride. It is fairly soluble in water and decomposes within a short time on exposure to air.

(*b*) The ester (III*a*) (23·4 g.) was added to a suspension of sodium hydride (5 g.) in ether (200 ml.), with stirring. The reaction started after a short time and intermittent cooling was necessary. When the exothermic reaction had subsided the mixture was refluxed for 6 hr., then cooled, acidified, washed with water and dried. Treatment as in (*a*) gave 13·2 g. (70%) of (IV*a*).

3-*Methoxy*-2-*phenyl*cyclo*hex*-2-*enone* (V*a*).—The diketone (IV*a*) was dissolved in methanol and allowed to react with ethereal diazomethane. Evaporation gave a crystalline residue which by recrystallization from benzene afforded short prisms of the cyclo*hexenone* (V*a*) (90%), m. p. 96—98° ($\lambda_{max.}$ 270 mμ; *E* 14,500) (Found : C, 76·9; H, 6·9. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%).

3-*Ethoxy*-2-*phenyl*cyclo*hex*-2-*enone*.—The diketone (IV*a*) (1·88 g.), in absolute ethanol (20 ml.) containing ethyl orthoformate (10 ml.), was refluxed for 5 hr. under nitrogen. The blue colour which was present during the reaction disappeared on cooling. Solid sodium hydrogen carbonate (0·5 g.) was added and the solvents were removed *in vacuo*. The residue was taken up in ether, washed with aqueous sodium hydroxide solution (5%) and water, and dried (Na_2SO_4). On evaporation of the solvent *in vacuo* the residue crystallized. Recrystallization from methyl*cyclo*hexane afforded the 3-*ethoxy-ketone* (1 g., 50%) as prismatic needles, m. p. 102° (Found : C, 77·6; H, 7·5. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Acidification of the alkaline washings afforded unchanged material.

The methyl and ethyl enol ethers are stable in air. They readily revert in acidic and basic solution to the corresponding diketone (IV*a*).

2-*Phenyl*cyclo*hex*-2-*enone* (VI*a*).—A suspension of the ketone (V*a*) (1 g.) in absolute ether (50 ml.) was added to a solution of lithium aluminum hydride (0·2 g.) in absolute ether (40 ml.) with cooling. The mixture was refluxed for 1 hr., then cooled with ice and decomposed as usual with dilute hydrochloric acid. Thus an oily residue was obtained which crystallized from hexane as prismatic needles, m. p. 95—96° (43 g., 50%). Mixed m. p.s of this compound and the corresponding dinitrophenylhydrazone with authentic samples (Ginsburg and Pappo, *loc. cit.*) showed no depression.

αα-*Dimethylglutaric Acid*.—This was synthesized from 4-cyano-2 : 2-dimethylbutaldehyde (Walker, *Chem. Abs.*, 1947, **41**, 1235; U.S.P. 2,409,086) by simultaneous oxidation and hydrolysis with nitric acid (Franke and Bueren, *Z. Naturforsch.*, 1950, **5***b*, 122). Walker's procedure (*loc. cit.*) for the synthesis of the aldehyde gave erratic results, the yields varying from 10 to 40%; once the (exothermic) reaction went out of control. The following modification gave reproducible results with yields of 50—60%. 50% Sodium hydroxide solution (3 ml.) was added to acrylonitrile (100 ml.), and then *iso*butaldehyde (60 g.), and the mixture was heated cautiously. When the reaction started the heating was discontinued without removing the heating mantle. When the spontaneous reaction subsided (0·5—1 hr.) the mixture was refluxed for *ca.* 1·5 hr., then cooled and neutralized with concentrated hydrochloric acid. Some filter

aid was added and the solution filtered from salt and polymeric material. The residue on the filter was washed thoroughly with ether and the combined filtrates were concentrated.

Ethyl αα-Dimethylglutarate (I*b*).—The foregoing crude acid (20 g.) was refluxed in absolute ethanol (100 ml.) and anhydrous benzene (100 ml.) containing 2 ml. of concentrated sulphuric acid until no more water collected at the top of the column. Isolation by the usual procedure and distillation gave 24·3 g. (95% yield) of the desired ester (Blaise, *Bull. Soc. chim.*, **1899**, **21**, 626).

Ethyl 6-*Cyano*-5-*keto*-2 : 2-*dimethyl*-6-*phenylhexanoate* (II*b*).—The condensation was carried out as in the preparation of (II*a*) (procedure *b*), with a solution of sodium (3·5 g., 0·15 mole) in absolute ethanol (41 ml.), benzyl cyanide (17·6 g., 0·1 mole), and (I*b*) (21·6 g.; 0·1 mole). Distillation gave some starting material and 21·8 g. (76%) of the *ester* (II*b*), b. p. 180—210°/1 mm. (Found: C, 71·2; H, 7·0. $C_{17}H_{21}O_3N$ requires C, 71·0; H, 7·3%).

Hydrolysis and decarboxylation of (II*b*), carried out as with (II*a*), afforded crystalline 5-*keto*-2 : 2-*dimethyl*-6-*phenylhexanoic acid*. Recrystallization from di*iso*propyl ether gave fine needles, m. p. 83—84° (Found: C, 72·1; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). This gave a *semicarbazone*, m. p. 179° (decomp.) (from ethanol) (Found: C, 62·2; H, 7·6; N, 14·4. $C_{15}H_{21}O_3N_3$ requires C, 61·9; H, 7·2; N, 14·4%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 168—169° (from ethanol) (Found: C, 58·2; H, 5·7; N, 13·8. $C_{20}H_{22}O_6N_4$ requires C, 58·0; H, 5·3; N, 13·5%). Its *ethyl* ester (III*b*), prepared in the same manner as (III*a*), in 80% yield, had b. p. 145°/1 mm. (Found: C, 73·3; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

4 : 4-*Dimethyl*-2-*phenyl*cyclo*hexane*-1 : 3-*dione* (IV*b*).—Best results were obtained when the ester (III*b*) was refluxed for 6 hr. with 2 equivs. of sodium hydride in anhydrous toluene. The mixture was carefully acidified with dilute hydrochloric acid, which gave the diketone (IV*b*) as a colourless crystalline precipitate. It was filtered off, washed with toluene and water, and dried. The combined toluene filtrate and washings were washed with water and 5% sodium hydroxide solution. The alkaline extracts were washed with ether and then acidified with 5% hydrochloric acid. The resultant oily precipitate was taken up in ether, washed with water, and dried ($MgSO_4$). Evaporation gave an oil which partly crystallized. Recrystallization from toluene afforded a further quantity of the diketone (IV*b*). The combined crops, recrystallized from toluene, had m. p. 210° (50% yield) (Found: C, 78·1; H, 7·8. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Evaporation of the neutral fraction gave only a negligible amount of starting material. The mother-liquor from the crystallization of the acidic fraction gave an oil which was not further investigated.

The dione (IV*b*) is soluble in dilute sodium carbonate solution and slightly soluble in aqueous sodium hydrogen carbonate It does not give a colour reaction with ferric chloride in alcohol or water.

3-*Methoxy*-6 : 6-*dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (V*b*) *and* 3-*Methoxy*-4 : 4-*dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (V*c*).—The diketone (IV*b*) was dissolved in methanol and allowed to react with ethereal diazomethane. The partly crystalline residue obtained on evaporation was recrystallized from hexane and then from methyl*cyclo*hexane. Thus, the *ketone* (V*b*) was obtained as stout prisms, m. p. 134—135° (60%) ($\lambda_{max.}$ 268 mμ; *E* 13,700) (Found: C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). The mother-liquor yielded, on evaporative distillation (120°/0·1 mm.), a mobile oil which crystallized at 0°. Recrystallization from hexane gave the *isomer* (V*c*), m. p. 37° ($\lambda_{max.}$ 263 mμ; *E* 12,000) (Found: C, 78·4; H, 8·0%).

The ketone (V*b*) is hydrolyzed more slowly than (V*c*) by boiling 5% aqueous sodium hydroxide.

4 : 4-*Dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (VI*b*).—Reduction of the ketone (V*b*), suspended in ether, with lithium aluminum hydride, as described above, gave an oil which afforded a 30% yield of the red 2 : 4-*dinitrophenylhydrazone*, m. p. 172—174° (from ethanol–ethyl acetate), of (VI*b*) (Found: C, 63·1; H, 5·3. $C_{20}H_{20}O_4N_4$ requires C, 63·2; H, 5·3%).

The low yields obtained in the reduction of (V*a*) and (V*b*) may well be due to the insolubility of those compounds in ether.

6 : 6-*Dimethyl*-2-*phenyl*cyclo*hex*-2-*enone* (VI*c*).—The ketone (V*c*) was more soluble in ether than either (V*a*) or (V*b*) and could, therefore, be reduced with lithium aluminum hydride *in solution*. The oily product was obtained in quantitative yield and afforded the orange 2 : 4-*dinitrophenylhydrazone*, m. p. 161—162° (from ethanol–ethyl acetate), of (VI*c*) in quantitative yield (Found: C, 63·3; H, 5·2%).

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367. *Complex Fluorides. Part I. The Structural Chemistry of Some Complex Fluorides of Potassium, Rubidium, Cæsium, Ammonium, and Thallium.*

By B. Cox and A. G. Sharpe.

The occurrence of the K_2SiF_6 (cubic), K_2GeF_6 (trigonal), and K_2MnF_6 (hexagonal) structures among complex fluorides of formula A_2BF_6 (where A is a large univalent cation) is discussed. When prepared at room temperature, K_2TiF_6, Rb_2TiF_6, Cs_2TiF_6, $(NH_4)_2TiF_6$, and Tl_2TiF_6 are isomorphous with K_2GeF_6. Hexagonal forms of K_2TiF_6 and Rb_2TiF_6, and cubic forms of K_2TiF_6, Rb_2TiF_6, Cs_2TiF_6, and Tl_2TiF_6 have been obtained by heating samples at 300—350°. Except in $(NH_4)_3FeF_6$, there is at present no evidence for hydrogen bonding as an important factor in complex fluorides containing the ammonium ion.

It was suggested (Sharpe, *J.*, 1953, 197) that for complex fluorides of formula A_2BF_6 (where A = K, Rb, Cs, NH_4, Tl) the two well-known structures of K_2SiF_6 and K_2GeF_6 are of nearly equal energy, and that their distribution is approximately a random one. We began a systematic search for further evidence in support of this hypothesis by examining the structures of the fluorotitanates; the recent publication of structural data for the complex fluorides K_2TiF_6, K_2PdF_6, Rb_2PdF_6, K_2MnF_6, Rb_2MnF_6, and Cs_2MnF_6, however, assists us considerably and prompts us to report our own work now and to summarise the present position in this field.

The K_2SiF_6, K_2GeF_6, and K_2MnF_6 structures may all be described (following Wells, "Structural Inorganic Chemistry," Oxford, 1945) as built up from close-packed layers of K and F atoms, with the Si, Ge, or Mn atoms in certain of the octahedral holes. In the cubic K_2SiF_6 structure, the layers are arranged in cubic close-packing (layer sequence ABC, ABC); in the ideal trigonal structure, from which K_2GeF_6 deviates slightly, the layers are arranged in hexagonal close-packing (sequence AB, AB); and in the hexagonal K_2MnF_6 structure (first described by Bode and Wendt, *Z. anorg. Chem.*, 1952, **269**, 165) the layers appear to be arranged in double hexagonal close-packing (sequence ABAC, ABAC). All available data for unit-cell dimensions of complex fluorides containing large univalent cations and silicon, germanium, titanium, manganese, nickel, palladium, or platinum are assembled in the Table; for details of the preparation of polymorphic forms by other authors, individual references should be consulted.

In the past, the deviations from ideal close-packing round the alkali-metal atoms in, *e.g.*, K_2GeF_6 and Rb_2GeF_6 have probably attracted too much attention; but it should be pointed out that similar minor deviations also exist in K_2PtF_6, K_2TiF_6, and Cs_2PuCl_6 (Zachariasen, *Acta Cryst.*, 1948, **1**, 268). Furthermore, since most of the other complex fluorides (some of which are very unstable) have been subjected only to partial examination by powder methods, departures from ideal close-packing may be quite common. Nevertheless, the irregular distribution of the K_2SiF_6, K_2GeF_6, and K_2MnF_6 structures, and the existence of some of the complex fluorides in three modifications, suggest that the three structures are energetically equivalent and that their distribution is a random one.

The similarity in unit-cell dimensions between $(NH_4)_2TiF_6$ and Rb_2TiF_6 suggests that hydrogen bonding plays no significant part in determining the structure of the former compound [cf. Vincent and Hoard (*loc. cit.*), who made a similar observation on $(NH_4)_2GeF_6$ and Rb_2GeF_6]. Ammonium hexafluoroferrate (Pauling, *J. Amer. Chem. Soc.*, 1924, **46**, 2738; Minder, *Z. Krist.*, 1937, **96**, 15; Rice, Turner, and Brydon, *Nature*, 1952, **169**, 749) remains the only ammonium complex fluoride in which the unit cell is very much smaller than that of the analogous rubidium compound. Since FeF_6^{3-} is the only complex fluoride ion of known structure in which magnetic properties unambiguously indicate the presence of "ionic" or weak covalent bonds (see Nyholm and Sharpe, *J.*, 1952, 3579, for discussion) there may be a correlation between the weakness of the iron–fluorine bonds and the strength of the hydrogen bonding between fluorine and nitrogen. It is hoped to provide further

evidence concerning the existence of such a correlation by the preparation of ammonium fluorocobaltate, $(NH_4)_3CoF_6$, and the determination of its unit-cell size and magnetic moment.

Unit-cell dimensions (in Å).

SiF_6	K_2	Rb_2	Cs_2	$(NH_4)_2$	Tl_2
Trigonal...	—	—	—	$a=5{\cdot}76$, $c=4{\cdot}77$ [13]	—
Cubic	$a=8{\cdot}13$,[1] $8{\cdot}17$ [10]	$a=8{\cdot}45$ [10]	$a=8{\cdot}87$,[10] $8{\cdot}89$ [1]	$a=8{\cdot}34$,[10] $8{\cdot}38$ [12]	$a=8{\cdot}56$,[10] $8{\cdot}60$ [11]
GeF_6					
Trigonal...	$a=5{\cdot}62$, $c=4{\cdot}65$ [7]	$a=5{\cdot}82$, $c=4{\cdot}79$ [8]	—	$a=5{\cdot}85$, $c=4{\cdot}77$ [7]	—
Hexagonal	$a=5{\cdot}71$, $c=9{\cdot}27$ [6]	$a=5{\cdot}94$, $c=9{\cdot}63$ [6]	—	—	—
Cubic	—	—	$a=8{\cdot}99$ [9]	—	—
TiF_6					
Trigonal...	$a=5{\cdot}71$, $c=4{\cdot}65$ [1, 15]	$a=5{\cdot}88$, $c=4{\cdot}78$ [1]	$a=6{\cdot}15$, $c=4{\cdot}96$ [1]	$a=5{\cdot}96$, $c=4{\cdot}82$ [1]	$a=5{\cdot}92$, $c=4{\cdot}84$ [1]
Hexagonal	$a=5{\cdot}75$, $c=9{\cdot}46$ [1]	$a=5{\cdot}91$, $c=9{\cdot}81$ [1]	—	—	—
Cubic	$a=8{\cdot}32$ [1]	$a=8{\cdot}49$ [1]	$a=8{\cdot}96$ [1]	—	$a=8{\cdot}46$ [1]
MnF_6					
Trigonal...	$a=5{\cdot}71$, $c=4{\cdot}65$ [5]	—	—	—	—
Hexagonal	$a=5{\cdot}70$, $c=9{\cdot}35$ [5]	$a=5{\cdot}85$, $c=9{\cdot}50$ [5]	—	—	—
Cubic	$a=8{\cdot}28$ [5]	$a=8{\cdot}43$ [5]	$a=8{\cdot}92$ [5]	—	—
NiF_6					
Cubic	$a=8{\cdot}11$ [14]	—	—	—	—
PdF_6					
Hexagonal	$a=5{\cdot}75$, $c=9{\cdot}51$ [4]	$a=5{\cdot}98$, $c=9{\cdot}70$ [1]	—	—	—
Cubic	—	$a=8{\cdot}57$ [4]	$a=9{\cdot}00$,[4] $9{\cdot}01$ [2]	—	—
PtF_6					
Trigonal...	$a=5{\cdot}76$, $c=4{\cdot}64$ [2, 3]	$a=5{\cdot}96$, $c=4{\cdot}83$ [2]	$a=6{\cdot}22$, $c=5{\cdot}01$ [2]	—	—

[1] Present work. [2] Sharpe, *J.*, 1953, 197. [3] Mellor and Stephenson, *Austral. J. Sci. Res.*, 1951, **4**, *A*, 406. [4] Hoppe and Klemm, *Z. anorg. Chem.*, 1952, **268**, 364. [5] Bode and Wendt, *ibid.*, **269**, 165. [6] Bode and Brockmann, *ibid.*, p. 173. [7] Hoard and Vincent, *J. Amer. Chem. Soc.*, 1939, **61**, 2849. [8] Vincent and Hoard, *ibid.*, 1942, **64**, 1233. [9] Wyckoff and Müller, *Amer. J. Sci.*, 1927, **13**, 347. [10] Ketelaar, *Z. Krist.*, 1935, **92**, 155. [11] Tabet, *Gazzetta*, 1933, **63**, 679. [12] Bozorth, *J. Amer. Chem. Soc.*, 1922, **44**, 1066. [13] Gossner and Kraus, *Z. Krist.*, 1934, **88**, 223. [14] Klemm and Huss, *Z. anorg. Chem.*, 1949, **258**, 221. [15] Siegel, *Acta Cryst.*, 1952, **5**, 683.

Experimental.—Fluorotitanates were obtained from titanium dioxide, hydrofluoric acid, and metal fluorides: Titanium was determined as dioxide; thallium in *thallous fluorotitanate* was determined as chromate after precipitation of the titanium [Found, for the K salt: Ti, 20·0. Calc. for K_2TiF_6: Ti, 20·0. Found, for the Rb salt: Ti, 14·5. Calc. for Rb_2TiF_6: Ti, 14·4. Found, for the Cs salt: Ti, 11·3. Calc. for Cs_2TiF_6: Ti, 11·2. Found, for the NH_4 salt: Ti, 24·1. Calc. for $(NH_4)_2TiF_6$: Ti, 24·2. Found, for the Tl salt: Tl, 70·7; Ti, 8·4. Tl_2TiF_6 requires Tl, 71·7; Ti, 8·4%].

The existence of polymorphic forms was investigated by heating small samples at temperatures between 275° and 350°; powder photographs of the residues were taken at room temperature. The potassium salt, after being heated at 350° for 24 hr., gave a powder pattern corresponding to a mixture of hexagonal and cubic forms. The structure of the rubidium salt was unchanged after 18 hr. at 275°; after 24 hr. at 300° the powder pattern was that of a mixture of hexagonal and cubic forms. At 300° the cæsium salt remained trigonal, but heating it at 350° for 24 hr. resulted in a change to the cubic structure. The ammonium salt decomposed completely at 275°. Thallous fluorotitanate became cubic after 24 hr. at 350°, and was still cubic after six weeks at room temperature.

The sample of rubidium fluoropalladate used had been prepared at 150° (*J.*, 1953, 197).

X-Ray powder photographs were taken with Cu-$K\alpha$ radiation; samples were filled into Pyrex capillaries, the " dry box " technique being used for Rb_2PdF_6, and the capillaries were sealed off with warm picein wax.

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University Chemical Laboratory, Cambridge [*Received, January 17th*, 1953.]

368. *Unsaturated Fatty Acids. Part I. The Synthesis of Erythrogenic (Isanic) and Other Acetylenic Acids.*

By H. K. Black and B. C. L. Weedon.

The structure (II) assigned to erythrogenic (isanic) acid has been confirmed by synthesis.

Oxidative coupling of a mixture of dec-9-ynoic acid (prepared by Barbier–Wieland degradation of undec-10-ynoic acid) and oct-1-en-7-yne (prepared from 6-chlorohex-1-yne) gave the expected three products, one of which, octadec-17-ene-9 : 11-diynoic acid, was isolated and identified with natural erythrogenic acid.

Of the naturally occurring unsaturated fatty acids, those possessing an unsaturated linkage separated from the carboxyl group by a chain of seven methylene groups constitute the main class (cf. Hilditch, *J.*, 1948, 243). The investigations to be described in this series of papers have as their initial objective the synthesis of these fatty acids from easily accessible intermediates of the type $HC{:}C{\cdot}[CH_2]_7{\cdot}X$, where X is carboxyl or a group readily converted into carboxyl. The present communication deals chiefly with the confirmation, by total synthesis, of the structure assigned to erythrogenic (isanic) acid.*

The tree *Onguekoa Gore* Engler (syn. *Ongokea klaineana* Pierre; also known by the native names Boleka and Isano), which is indigenous to Equatorial Africa, bears fruits with kernels yielding *ca.* 60% of a viscous oil on extraction. From this Hébert (*Bull. Soc. chim.*, 1896, **15**, 935; *Compt. rend.*, 1896, **122**, 1550) isolated a fatty acid which he believed to belong to the C_{14} series. More recently Steger and van Loon (*Fette u. Seifen*, 1937, **44**, 243) fractionated the ethyl esters of the total fatty acids and found that these contained practically no C_{14} acid fraction, but consisted mainly of acids of the C_{18} series; a monoethylenic, diacetylenic acid was separated by crystallisation and shown to give stearic acid on catalytic reduction. Shortly afterwards the isolation of this unsaturated acid by means of its ether-soluble lead salt was reported by Castille (*Annalen*, 1940, **543**, 104), who ozonised both the acid and its ethyl ester and concluded that the former must have one of the structures (I) and (II) :

(I) $CH_2{:}CH{\cdot}C{:}C{\cdot}[CH_2]_4{\cdot}C{:}C{\cdot}[CH_2]_7{\cdot}CO_2H$ $\qquad$ $CH_2{:}CH{\cdot}[CH_2]_4{\cdot}C{:}C{\cdot}C{:}C{\cdot}[CH_2]_7{\cdot}CO_2H$ (II)

These deductions were confirmed by Steger and van Loon (*Rec. Trav. chim.*, 1940, **59**, 1156; cf. Doucet and Fauve, *Compt. rend.*, 1942, **215**, 533) who favoured the second formula. Subsequent investigations by Castille (*Bull. Acad. Roy. Méd. Belg.*, 1941, **6**, 152) are said to have proved structure (II) correct. Unfortunately full experimental details of these degradative studies have not been published by either the Dutch or the Belgian workers. However, a comparison of the ultra-violet light-absorption properties recorded by Castille (1940) for the natural acid, with those determined later with authentic vinylacetylenes, shows that the structure (I) is inadmissible (Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998). As was observed by Hébert (*loc. cit.*), this unsaturated fatty acid is readily converted into a bright red insoluble polymer (see below). For this reason Castille proposed the name " erythrogenic acid," but Steger and van Loon refer to the same compound as " isanic acid," the term first introduced by Hébert for his " C_{14} acid."

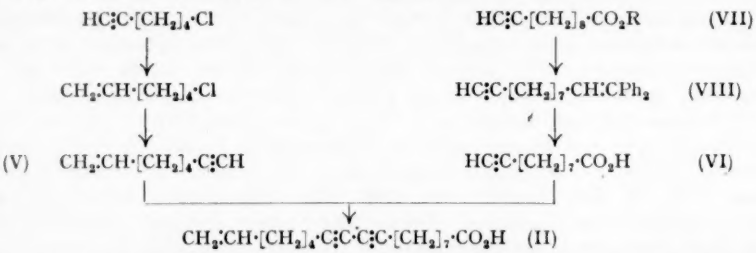
Many statements have been made that boleka (isano) oil has good drying properties. These claims have, however, been refuted by Steger and van Loon (*Rec. Trav. chim.*, 1941, **60**, 342), and interest in erythrogenic acid therefore centres mainly on its unusual constitution. A few other acetylenic and polyacetylenic compounds have been encountered in Nature (Steger and van Loon, *Rec. Trav. chim.*, 1933, **52**, 593; Anchell, *J. Amer. Chem. Soc.*, 1952, **74**, 1588; Celmer and Solomons, *ibid.*, p. 1870; Ligthelm, Schwartz, and von Holdt, *J.*, 1952, 1088; Anet, Lythgoe, Silk, and Trippett, *Chem. and Ind.*, 1952, 757; Williams, Smirnov, and Gol'mov, *J. Gen. Chem., Moscow*, 1935, **5**, 1195; Sörensen and

* A preliminary account of this work was given in *Chem. and Ind.*, 1953, 40.

Steen, *Annalen*, 1941, **549**, 80; Stavolt and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 1567; Baalsrud, Stavolt, Holme, Nestvold, Plíva, Sörensen, and Sörensen, *ibid.*, 1952, **6**, 883; Sörensen, *Chem. and Ind.*, 1953, 240), and recently the structures of both tariric acid (III) (Lumb and Smith, *J.*, 1952, 5032) and 8-*cis*-αβ-dihydromatricaria ester (IV) (Christensen and Sörensen, *Acta Chem. Scand.*, 1952, **6**, 893) were substantiated by synthesis.

(III) $CH_3\cdot[CH_2]_{10}\cdot C{:}C\cdot C{:}C\cdot[CH_2]_4\cdot CO_2H$ $CH_3\cdot CH{:}CH\cdot C{:}C\cdot C{:}C\cdot CH_2\cdot CH_2\cdot CO_2Me$ (IV)

Conjugated diacetylenes ($R\cdot C{:}C\cdot C{:}C\cdot R$) may be prepared by a variety of methods involving oxidative coupling of a mono-substituted acetylene ($R\cdot C{:}CH$) (cf. Jones, *Ann. Reports*, 1944, **41**, 148; Black, Horn, and Weedon, unpublished), and also by alkylation of metal derivatives of diacetylene (Armitage, Jones, and Whiting, *J.*, 1951, 144). The route envisaged for the synthesis of erythrogenic acid consisted of the oxidation, in the presence of cuprous ammonium chloride (cf. Zal'kind and Fundyler, *Ber.*, 1936, **69**, 128), of a mixture of oct-1-en-7-yne (V) and dec-9-ynoic acid (VI), both symmetrical and unsymmetrical coupling of the two components being expected to take place.



A convenient route to the decynoic acid (VI) was developed from undec-10-enoic acid, which is readily available commercially, being prepared from ricinoleic acid, and has previously been synthesised (Gaubert, Linstead, and Rydon, *J.*, 1937, 1971). The methods described by earlier workers for converting undecenoic acid into undecynoic acid (VII; R = H), by bromination and subsequent dehydrobromination, were examined, and the overall yield was raised to 60%. Reaction of ethyl undecynoate (VII; R = Et) with phenylmagnesium bromide gave a tertiary alcohol which was dehydrated to the hydrocarbon (VIII) in 70% overall yield. With chromic acid this furnished (58%) the required decynoic acid (VI), oxidation occurring preferentially at the double bond. An analogous series of reactions was carried out starting with ethyl undecynoate and methylmagnesium iodide. Dehydration of the resulting tertiary alcohol gave (56%) a mixture (1 : 2) of 2-methyldodec-1- and -2-en-11-yne, which on oxidation yielded decynoic acid (42%).

Few examples have previously been recorded of similar Barbier–Wieland degradations with unsaturated fatty acids. Oleic acid (Skraup and Schwamberger, *Annalen*, 1928, **462**, 135) and several ω-*cyclo*pent-2′-enyl acids (Buu-Hoï, *Ann. Chim.*, 1944, **19**, 446) give the corresponding lower homologues, but erucic (docos-13-enoic) acid is stated to yield 12 : 13-dihydroxyheneicosanoic acid (Buu-Hoï and Janicaud, *Bull. Soc. chim.*, 1946, 147). It has now been shown that Barbier–Wieland degradation of ethyl undec-10-enoate gives dec-9-enoic acid in 50% yield. This acid occurs naturally in milk fat and in sperm-head oil (Hilditch, " The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1947).

The second component, oct-1-en-7-yne (V), was prepared in the following manner. 6-Chlorohex-1-yne (Newman and Wotiz, *J. Amer. Chem. Soc.*, 1949, **71**, 1292) was partially hydrogenated in the presence of a palladium catalyst to 6-chlorohex-1-ene (90%). This was converted into the corresponding iodide which, without purification, was condensed with sodium acetylide giving the required octenyne (V) in 70% yield (based on chlorohexene).

To establish the conditions for the formation of diacetylenic fatty acids of the required type, preliminary experiments were carried out on the cross-coupling of undec-10-ynoic acid (VII; R = H) with hex-1-yne and oct-1-yne. In both cases the expected mixture

of three products was produced, but these were readily separated and under optimum conditions heptadecadiynoic (IX; $n = 3$, $m = 8$) and nonadecadiynoic acid (IX; $n = 5$,

$$CH_3\cdot[CH_2]_n\cdot C{:}C\cdot C{:}C\cdot[CH_2]_m\cdot CO_2H \quad (IX)$$

$m = 8$) were isolated each in 30% yield (based on undecynoic acid). Similar coupling of oct-1-yne with the decynoic acid (VI) led to dihydroerythrogenic acid (IX; $n = 5$, $m = 7$) which was obtained as a crystalline solid (32%). The preparation of this acid from natural erythrogenic acid has been claimed by Castille (*loc. cit.*) but no physical properties were reported.

The structures of the diacids (X; $m = 7$) and (X; $m = 8$), formed as by-products in the above reactions by self-coupling of the decynoic and undecynoic acids respectively, were confirmed by catalytic hydrogenation to 1 : 20-eicosane- and 1 : 22-docosane-dioic acid respectively.

$$HO_2C\cdot[CH_2]_m\cdot C{:}C\cdot C{:}C\cdot[CH_2]_m\cdot CO_2H \quad (X)$$

Cross-coupling of the octenyne (V) with the decynoic acid (VI) was next attempted and afforded octadec-17-ene-9 : 11-diynoic acid (II) in 30% yield. Its melting point was identical with that of a specimen of natural erythrogenic acid (for which the authors are greatly indebted to Dr. E. M. Meade), and no depression was observed on admixture (see Table); the identity was confirmed by comparison of the *p*-bromophenacyl esters and 2-hydroxyethylamides. Ozonolysis of the synthetic acid gave formaldehyde (36%).

	Synthetic	Natural	Mixture
Erythrogenic acid	—	39° [1]	—
„ „	—	39·5 [2]	—
„ „	38·4—39·0°	38·5—39·0 [3]	38·5—39·0°
2-Hydroxyethylamide	67·0—68·0	67·0—68·0 [3]	67·0—68·0
p-Bromophenacyl ester	40·5—41·5	41·0—42·0 [4]	40·5—41·5

[1] Steger and van Loon, *Rec. Trav. chim.*, 1940, **59**, 1156. [2] Castille, *Annalen*, 1940, **543**, 104. [3] Determined after repurification of samples supplied by Dr. E. M. Meade. [4] Prepared from Dr. Meade's specimen of the natural acid.

The ultra-violet light absorption properties of the two acids and related compounds are tabulated below. The position and intensity of the absorption maxima of synthetic erythrogenic acid agree well with the corresponding data for heptadeca-10 : 12-, nonadeca-10 : 12-, and octadeca-9 : 11-diynoic acids, and other authentic conjugated diacetylenes. The natural acid, however, exhibits a slightly more complex spectrum; the bands characteristic of the synthetic diyne acids are present, together with others of longer wave-lengths,

Light absorption of diacetylenes (*max. in* Å; ε *in parentheses*).

Octa-5 : 7-diyne [1]	2280 (440)	2390 (390)	2540 (240)		
Heptadeca-10 : 12-diynoic acid	2280 (575)	2350 (445)			
Nonadeca-10 : 12-diynoic acid	2270 (470)	2370 (320)			
Octadeca-9 : 11-diynoic acid *	2280 (430)	2360 (320)			
„ 2-hydroxyethylamide †	2270 (550)	2390 (430)	2550 (200)		
Synthetic erythrogenic acid	2270 (370)	2370 (340)	2540 (40)		
Natural „ ‡	2270 (480)	2400 (480)	2550 (384)	2670 (300)	2800 (260)
„ „ [2]	2275 (1167)	2400 (870)	2530 (700)	2666 (870)	2820 (700)
Propenyldiacetylene [1]	2300 (2250)	2380 (5000)	2510 (10,000)	2640 (14,000)	2800 (11,000)
2-Hydroxyethylamide of synthetic erythrogenic acid	2270 (640)	2380 (444)	2510 (181)		
2-Hydroxyethylamide of natural erythrogenic acid ‡	2270 (650)	2380 (438)	2510 (228)		
*iso*Butylamide of synthetic erythrogenic acid	2260 (510)	2380 (378)	2510 (214)	2550 (230)	

* Also 2230 Å, ε = 430. † Also 2480 Å, ε = 200. ‡ Determined after repurification of samples supplied by Dr. E. M. Meade.

[1] Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998. [2] Castille, *Annalen*, 1940, **543**, 104.

suggesting that, even after careful purification, the natural acid still contains a small amount (*ca.* 2—3%) of an impurity with an enediyne chromophore. This contaminant has recently been isolated by Meade and named bolekic acid (cf. Jones, Whiting, Armitage,

Cook, and Entwistle, *Nature*, 1951, **168**, 900). (Castille's light-absorption data for natural erythrogenic acid indicate that his sample contained *ca.* 6% of bolekic acid.) The hydroxyethylamides, which are more readily purified than the parent acids, exhibit almost identical light absorption properties.

Crystals of all the synthetic diacetylenic acids and their derivatives described above exhibit the remarkable photolability observed previously with natural erythrogenic acid (Hébert; Steger and van Loon; Castille; *locc. cit.*) and some other diacetylenes (Jones and Whiting *et al.*, *J.*, 1952, 1998). Natural and synthetic erythrogenic acid both give, on irradiation, even in high vacuum, a vivid red polymer insoluble in the common organic solvents and in alkali. The same effect is observed with the derivatives, though the *p*-bromophenacyl ester is comparatively stable. The natural acid is slightly more sensitive to light than the synthetic, probably owing to contamination with bolekic acid. The polymer has the same composition as the parent acid (Steger and van Loon, and Castille, *locc. cit.*).

On exposure to daylight, the crystal surfaces of the majority of the other diacetylenic acids now reported become blue; this colour changes to red on addition of methanol or other solvents which dissolve the unchanged diacetylenes, but not the polymer. A similar reddening frequently takes place on prolonged exposure to light and, at least in one instance (nonadeca-10 : 12-diynoic acid), a reversible change from blue to red occurs simply on warming from 0° to *ca.* 30°. The formation of the initial colours under the influence of light seems to be accentuated by rise in temperature. All these diacetylenes are quite unaffected by light when in solution; the solid urea complex of erythrogenic acid is also stable.

The structure of these coloured polymers is obscure. It has, however, been suggested that they are formed by cross-linking of poly-yne chains, which in a favourable crystal lattice are perhaps held close together, as a consequence of photochemical activation (Jones, Whiting, *et al.*, *loc. cit.*). It is proposed to examine these phototropic and thermotropic changes in more detail.

This opportunity is taken to report the synthesis of octadec-9-ynoic (stearolic) and heptadec-9-ynoic acid from intermediates developed in the investigations described above. Treatment of the Grignard reagent from the mixture of methyldodecenynes with *n*-octyl and *n*-hexyl toluene-*p*-sulphonate gave, respectively, mixtures of the methyleicosenynes (XI) and (XII), and the corresponding methyloctadecenynes. (Hex-1-yne and oct-1-yne were similarly converted into dec-5-yne and tetradec-5-yne in 44 and 34% yield respectively.) Oxidation of these hydrocarbon mixtures with chromic acid led to stearolic (XIII) and hexadec-9-ynoic acid in poor yield. The hydrogenation of stearolic to oleic acid over a lead-poisoned palladium catalyst (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) will be described in a later publication.

(XI) $CH_3 \cdot [CH_2]_7 \cdot C{:}C \cdot [CH_2]_7 \cdot CH{:}CMe_2$ $CH_3 \cdot [CH_2]_7 \cdot C{:}C \cdot [CH_2]_8 \cdot CMe{:}CH_2$ (XII)

$CH_3 \cdot [CH_2]_7 \cdot C{:}C \cdot [CH_2]_7 \cdot CO_2H$ (XIII)

Experimental

Yields are based on the total amount of acetylenes used.

Light absorptions were determined on alcohol solutions of freshly purified samples.

As far as possible the crystalline diacetylenes were screened from light.

2-Hydroxyethylamides were prepared by the method of Swern, Stutzman, and Roe (*J. Amer. Chem. Soc.*, 1949, **71**, 3017).

Undec-10-ynoic Acid (VII; R = H).—Commercial undec-10-enoic acid was distilled and the fraction, b. p. 155—157°/10 mm., m. p. 24·5—25·0°, was collected. Bromination of the acid in light petroleum (b. p. 60—80°) (previously treated with excess of bromine, and then washed with saturated sodium hydrogen carbonate solution, dried, and distilled) by the method of Myddleton and Barratt (*J. Amer. Chem. Soc.*, 1927, **49**, 2258) gave 10 : 11-dibromoundecanoic acid (70%), m. p. 37—38·5° (*idem*, *loc. cit.*, give m. p. 38·5°). Dehydrobromination by the procedure of Jeffery and Vogel (*J.*, 1948, 674) gave undec-10-ynoic acid (88%), b. p. 178—184°/15 mm., m. p. 43° (Krafft, *Ber.*, 1896, **29**, 2232, gives m. p. 42·5—43°).

Use of chloroform or carbon tetrachloride (cf. Jeffery and Vogel, *loc. cit.*) for the bromination

was unsatisfactory; the crude product solidified slowly and gave poor yields of the acetylenic acid on dehydrobromination.

Ethyl Undec-10-enoate and Ethyl Undec-10-ynoate.—Esterification of undecenoic acid by Myddleton and Barratt's method (*loc. cit.*) gave the ethyl ester, b. p. 127—130°/10 mm. Ethyl undecynoate, prepared similarly in 83% yield, had b. p. 80—85°/0·1 mm., n_D^{22} 1·4450 (Jeffery and Vogel, *loc. cit.*, give b. p. 142°/13 mm., n_D^{20} 1·4480). The structure of the latter ester was confirmed by hydrolysis with aqueous alkali to undec-10-ynoic acid, m. p. and mixed m. p. 43° (90%).

1 : 1-*Diphenylundec-10-yn-1-ol and* 1 : 1-*Diphenylundec-1-en-10-yne* (VIII).—Ethyl undec-10-ynoate (100 g.) in ether (500 c.c.) was added dropwise at 20° to a stirred solution of phenylmagnesium bromide (from 41 g. of magnesium and 260 g. of bromobenzene) in ether (500 c.c.). The mixture was heated under reflux for 2½ hr. The Grignard complex was decomposed by the addition of ice and 2N-sulphuric acid. Isolation in the usual manner gave the alcohol which was dehydrated without purification by heating to 220° for ½ hr. (cf. Skraup and Schwamberger, *Annalen*, 1928, **462**, 135). Distillation gave 1 : 1-*diphenylundec-1-en-10-yne* (100 g., 70%), b. p. 240—245°/17 mm., 152°/0·02 mm., n_D^{21} 1·5620 (Found: C, 91·2; H, 8·4. $C_{23}H_{26}$ requires C, 91·3; H, 8·7%). Light absorption: max., 2510 Å (ε 18,000). The hydrocarbon gave a precipitate with ammoniacal cuprous chloride.

2-*Methyldodec-11-yn-2-ol.*—Reaction of ethyl undec-10-ynoate (125 g.) with methylmagnesium iodide (from 50 g. of magnesium) gave the *alcohol* (100 g.), b. p. 77°/0·06 mm., n_D^{19} 1·4601 (Found: C, 79·4; H, 12·6. $C_{13}H_{24}O$ requires C, 79·5; H, 12·3%).

2-*Methyldodec-2-en-11-yne and* 2-*Methyldodec-1-en-11-yne.*—A mixture of phosphorus oxychloride (3·2 g.), pyridine (35 c.c.; dried over KOH), and toluene (63 c.c.; dried over Na) was added during 35 min. to a stirred and cooled solution of 2-methyldodec-11-yn-2-ol (10·0 g.) in toluene (48 c.c.). The mixture was heated to 90—95° for 45 min., then cooled and poured on ice. Isolation of the product in the usual manner gave the mixture of hydrocarbons (5·0 g., 56%), b. p. 49°/0·1 mm., n_D^{20} 1·4530 (Found: C, 87·7; H, 12·7. Calc. for $C_{13}H_{22}$: C, 87·5; H, 12·5%). Determination of *iso*propenyl end-groups by the semi-quantitative infra-red method (Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915) showed that the mixture contained *ca.* 30% of 2-methyldodec-1-en-11-yne.

Dehydration with formic acid, as described for the diphenylundecenol below, gave the same yield of hydrocarbons, but the product was contaminated with a small amount of a ketone (2 : 4-dinitrophenylhydrazone) formed, presumably, by hydration of the triple bond.

Dec-9-ynoic Acid (VI).—(*a*) A solution of chromium trioxide (17·0 g.) in water (20 c.c.) was added during 2½ hr. to a well stirred, warm (55—60°) solution of 1 : 1-diphenylundec-1-en-10-yne (25·0 g.) in acetic acid (250 c.c.). After the mixture had been stirred overnight at 20°, most of the solvent was evaporated under reduced pressure. The residue was warmed (steam-bath) for 1 hour with 2N-sulphuric acid (400 c.c.), then cooled and diluted with a saturated aqueous solution of sodium chloride (600 c.c.). Isolation of the acidic product in the usual way gave *dec-9-ynoic acid* (8·0 g., 58%), b. p. 88°/0·1 mm., n_D^{27} 1·4565, which crystallised in long needles, m. p. 22° (C, 71·5; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). The p-*bromophenacyl* ester crystallised from alcohol in plates, m. p. 75° (Found: C, 59·4; H, 6·1. $C_{18}H_{21}O_3Br$ requires C, 59·2; H, 5·8%).

A slightly lower yield of the acid was obtained by oxidising the hydrocarbon in acetone at 20° with chromic acid.

(*b*) Similar oxidation of the mixture of 2-methyldodec-2-en-11-yne and 2-methyldodec-1-en-11-yne in acetic acid gave dec-9-ynoic acid in 42% yield. The *p*-bromophenacyl ester had m. p. and mixed m. p. 75°.

1 : 1-*Diphenylundec-10-en-1-ol and* 1 : 1-*Diphenylundeca-1 : 10-diene.*—Reaction of ethyl undecenate (50·0 g.) with phenylmagnesium bromide (from 14·6 g. of magnesium and 87 g. of bromobenzene), in the manner described for the corresponding acetylene, gave the alcohol as a yellow oil. The crude product was divided into two equal portions which were dehydrated without purification as described below:

(i) (cf. Buu-Hoï, *Ann. Chim.*, 1944, **19**, 446). A mixture of the alcohol and formic acid (98—100%; 70 c.c.) was heated under reflux for 1¼ hr., then cooled and poured into water (400 c.c.). Isolation of the product with benzene and distillation gave 1 : 1-*diphenylundeca-1 : 10-diene* (30·0 g., 83% overall), b. p. 228—230°/12—14 mm., n_D^{21} 1·5545 (Found: C, 90·9; H, 9·3. $C_{23}H_{28}$ requires C, 90·8; H, 9·2%). Light absorption: max., 2510 Å (ε 20,000).

(ii) The crude alcohol was heated to 200° for 30 min. and then distilled, giving the hydrocarbon (29·0 g., 80% overall), b. p. 223—225°/10 mm., n_D^{20} 1·5540.

Dec-9-enoic Acid.—(i) A solution of chromium trioxide (19·0 g.) in water (20 c.c.) was added during 1½ hr. with vigorous stirring to a solution of 1 : 1-diphenylundeca-1 : 10-diene (25·0 g.) in glacial acetic acid (250 c.c.) at 35°. After a further ½ hour's stirring acetic acid (*ca.* 70 c.c.) was removed under reduced pressure and 2N-sulphuric acid (500 c.c.) was added to the residue. Extraction of the product with benzene and isolation of the acidic fraction furnished dec-9-enoic acid (8·5 g., 63%), b. p. 158—163°/21 mm., n_D^{21} 1·4485 (Found : C, 70·7; H, 10·6%; equiv., 164. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·7%; equiv., 170) (Toyama and Tsuchiya, *J. Chem. Soc., Japan*, 1935, **56**, 1313, give b. p. 143—148°/15 mm., n_D^{20} 1·4488, for the natural acid). The *p*-bromophenacyl ester crystallised from aqueous alcohol in plates, m. p. 58° (Found : C, 58·3; H, 6·1. Calc. for $C_{18}H_{23}O_3Br$: C, 58·8; H, 6·3%) (Baudart, *Bull. Soc. chim.*, 1946, 85, gives m. p. 57·5°).

(ii) Oxidation of the hydrocarbon (10·0 g.) in acetone (20 c.c.) (previously treated with excess of $KMnO_4$ and dried over K_2CO_3) by addition (2½ hr.) of a solution of chromium trioxide (7·5 g.) and concentrated sulphuric acid (6·5 c.c.) in water (21 c.c.) gave dec-9-enoic acid (2·5 g., 44%), b. p. 158—165°/16 mm., n_D^{21} 1·4485. The *p*-bromophenacyl ester had m. p. 58°, undepressed on admixture with the specimen described above.

Heptadeca-10 : 12-diynoic Acid (IX; $n = 3$, $m = 8$).—A solution of hex-1-yne (2·5 g.) and undec-10-ynoic acid (5·0 g.) in alcohol (90 c.c.) was added to a solution of cuprous chloride (6·0 g.) and ammonium chloride (18·0 g.) in hydrochloric acid (90 c.c.; 0·08N) in a 500-c.c. flask. The flask was connected to an oxygen reservoir and shaken until absorption ceased. The resulting light green suspension was treated with 2N-hydrochloric acid (200 c.c.), and then shaken with ether, whereupon two clear layers were obtained. The ethereal layer was washed with water and extracted with 2N-sodium hydroxide. The alkaline extract was acidified with 2N-hydrochloric acid, and the acidic fraction of the product thus liberated was isolated with ether, giving a solid (6·6 g.). Distillation from a short-path still gave (i) a yellow oil (1·0 g.), b. p. 70° (bath-temp.)/10^{-5} mm., which was not examined, and (ii) a solid (2·2 g., 30%), b. p. 110° (bath-temp.)/10^{-5} mm., m. p. 39—41°. Recrystallisation from aqueous alcohol gave *heptadeca-10 : 12-diynoic acid* as leaflets, m. p. 40·5—41° (Found : C, 77·9; H, 9·9%; equiv., 266. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%; equiv., 262. Found : hydrogen no. 69, equiv. to 3·8 double bonds). Light absorption : see Table. Crystallisation from alcohol of the solid residue (3·3 g.) from the distillation gave *docosa-10 : 12-diynedioic acid* as plates, m. p. 112° (Found : C, 72·85; H, 9·5. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·5%). Light absorption : max., 2260, 2380, 2510, and 2560 Å (ε 410, 360, 180, and 180 respectively). The *di*-p-*bromophenacyl* ester crystallised from alcohol in plates, m. p. 94° (Found : C, 60·6; H, 6·3. $C_{38}H_{44}O_6Br_2$ requires C, 60·4; H, 5·9%).

From the neutral fraction of the reaction product dodeca-5 : 7-diyne (2·0 g.) was isolated and had b. p. 113°/10 mm., n_D^{19} 1·4890 (Danehy and Nieuwland, *J. Amer. Chem. Soc.*, 1936, **58**, 1609, give b. p. 104°/8 mm.).

The use in the coupling reaction of heterogeneous solutions, or of catalytic amounts of cuprous ammonium chloride, was found unsatisfactory.

Docosanedioic Acid.—A solution of docosa-10 : 12-diynedioic acid (250 mg.) in alcohol (30 c.c.) was shaken with Adams' catalyst (10 mg.) in an atmosphere of hydrogen until absorption was complete (78 c.c. at 22°/765 mm., equiv. to 4·5 double bonds). Removal of catalyst and solvent, and crystallisation of the residue twice from alcohol, gave the saturated diacid as plates, m. p. 126° (Found : C, 71·3; H, 11·4. Calc. for $C_{22}H_{42}O_4$: C, 71·3; H, 11·4%) (Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 670, give m. p. 123—124°).

Nonadeca-10 : 12-diynoic Acid (IX; $n = 5$, $m = 8$).—Oxidation of oct-1-yne (3·5 g.) and undec-10-ynoic acid (5·0 g.) in alcohol (90 c.c.) and hydrochloric acid (90 c.c.; 0·08N), in the presence of cuprous ammonium chloride (from 6 g. of cuprous chloride and 18 g. of ammonium chloride), gave : (i) *Nonadeca-10 : 12-diynoic acid* (2·1 g., 32%), b. p. 130° (bath-temp.)/10^{-3} mm., which crystallised from aqueous alcohol in needles, m. p. 42—43° (Found : C, 78·7; H, 10·7. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%. Found : hydrogen no., 81, equiv. to 3·6 double bonds). Light absorption : see Table. The *p*-bromophenacyl ester had m. p. 57°. (ii) Docosa-10 : 12-diynedioic acid (1·0 g.), m. p. and mixed m. p. 112°.

Octadeca-9 : 11-diynoic Acid (*Dihydroerythrogenic Acid*) (IX; $n = 5$, $m = 7$).—Oxidation in the usual manner of oct-1-yne (3·2 g.) and dec-9-ynoic acid (4·5 g.) in alcohol (75 c.c.) and hydrochloric acid (75 c.c.; 0·08N) containing cuprous ammonium chloride (from 5·5 g. of cuprous chloride and 16·5 g. of ammonium chloride) gave : (i) *Octadec-9 : 11-diynoic acid* (2·4 g., 32%), b. p. 145° (bath-temp.)/10^{-4} mm., which crystallised from aqueous alcohol in needles, m. p. 46·0—46·5° (Found : C, 78·5; H, 10·7. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%.

Found: hydrogen no., 71, equiv. to 3·9 double bonds). Light absorption: see Table. The p-*bromophenacyl* ester crystallised from aqueous alcohol in plates, m. p. 58·5° (Found: C, 65·5; H, 6·9. $C_{26}H_{33}O_3Br$ requires C, 65·9; H, 7·0%). The 2-*hydroxyethylamide* crystallised from aqueous acetone in plates, m. p. 70—71° (Found: C, 75·6; H, 10·7. $C_{20}H_{33}O_2N$ requires C, 75·3; H, 10·4%). Light absorption: see Table. (ii) *Eicosa*-9: 11-*diynedioic acid* (3·0 g.) which crystallised from alcohol in plates (needles from dilute solution), m. p. 120° (Found: C, 71·9; H, 9·1. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%). The *di*-p-*bromophenacyl* ester crystallised from alcohol in plates, m. p. 104° (Found: C, 59·2; H, 5·7. $C_{36}H_{40}O_6Br_2$ requires C, 59·4; H, 5·5%). (iii) Hexadeca-7: 9-diyne (2·8 g.), b. p. 110°/0·5 mm., n_D^{23} 1·4928.

Stearic Acid.—A solution of octadeca-9: 11-diynoic acid (250 mg.) in alcohol (20 c.c.) was shaken in hydrogen in the presence of Adams' catalyst (10 mg.) until absorption was complete. Removal of catalyst and solvent and crystallisation of the residue from alcohol gave stearic acid, m. p. 68—69°, undepressed on admixture with an authentic specimen.

Eicosanedioic Acid.—A solution of eicosa-9: 11-diynedioic acid (0·3 g.) in alcohol (40 c.c.) was shaken with Adams' catalyst (15 mg.) in an atmosphere of hydrogen until absorption was complete (H_2 absorbed, 87 c.c. at 19°/761 mm., equiv. to 4·0 double bonds). Removal of catalyst and solvent and crystallisation of the residue twice from alcohol gave the saturated diacid, m. p. 119·5—120·5° (Found: C, 70·3; H, 11·1. Calc. for $C_{20}H_{38}O_4$: C, 70·2; H, 11·2%) (*idem, loc. cit.*, give m. p. 119—121°).

6-*Chlorohex*-1-*ene.*—A solution of 6-chlorohex-1-yne (40·0 g.) (prepared in 80% yield by the method of Newman and Wotiz, *J. Amer. Chem. Soc.*, 1949, **71**, 1292) in methyl acetate (200 c.c.) was shaken in an atmosphere of hydrogen in the presence of a palladium–calcium carbonate catalyst (4·0 g.; 0·3% of Pd). When 1 mol. of hydrogen had been absorbed (9 l. at 20°/780 mm.), the reaction was interrupted, the catalyst was filtered off, and the solvent was evaporated (through a 12 × 1″ Fenske column). Distillation of the residue in small batches from a Kon flask furnished 6-*chlorohex*-1-*ene* (35 g.), b. p. 128—130°, n_D^{24} 1·4320—1·4330 (Found: C, 60·7; H, 9·5; Cl, 30·2. $C_6H_{11}Cl$ requires C, 60·7; H, 9·4; Cl, 29·9%). The product, unlike the starting material, gave no silver salt. The physical constants were unaltered after fractionation of the chlorohexene through a Stedman column (15 × 2 cm.), but about a third of the material was polymerised in the process.

Oct-1-*en*-7-*yne* (V).—A solution of 6-chlorohex-1-ene (44·0 g.) and sodium iodide (100 g.) in acetone (500 c.c.) was heated under reflux with vigorous stirring overnight. The mixture was then cooled and water was added to dissolve the sodium chloride deposited and to precipitate the 6-iodohex-1-ene. This was isolated with ether in the usual way, and washed thoroughly in pentane solution with water, and the solution was dried ($MgSO_4$) and evaporated. Without further purification the crude 6-iodohexene in ether (100 c.c.) was added during 2½ hr. to a suspension in liquid ammonia (1 l.) of sodium acetylide (prepared from 30·0 g. of sodium *via* sodamide; cf. Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120). The mixture was stirred for 3 hr. and then kept overnight, most of the ammonia being allowed to evaporate. Water was added (in an atmosphere of nitrogen) and the product was extracted with ether. The ethereal extract was washed with sulphuric acid (2N) and then water, dried, and evaporated (12 × 1″ Fenske column). Distillation of the residue gave *oct*-1-*en*-7-*yne* (28·0 g.) as a very volatile liquid, b. p. 122°, n_D^{20} 1·4310—1·4325 (Found: C, 88·0; H, 11·0. C_8H_{12} requires C, 88·8; H, 11·2%).

Octadec-17-*ene*-9: 11-*diynoic Acid* (*Erythrogenic or Isanic Acid*) (II).—Oxidation in the usual manner of oct-1-en-7-yne (6·6 g.) and dec-9-ynoic acid (10·0 g.) in alcohol (100 c.c.) and hydrochloric acid (100 c.c.; 0·08N) containing cuprous ammonium chloride (from 12 g. of cuprous chloride and 36 g. of ammonium chloride) gave a crude product which was separated into neutral and acidic fractions. Distillation of the latter (12·5 g.) from short-path still yielded: (i) A liquid (1·9 g.), b. p. 100° (bath-temp.)/10^{-3} mm., which was not examined. (ii) A liquid (5·1 g.), b. p. 140° (bath-temp.)/10^{-3} mm., which solidified to a wax, m. p. 32—35°. Redistillation gave a solid (4·7 g.), m. p. 37·5—38·5°. Four crystallisations from light petroleum (b. p. 60—80°) yielded octadec-17-ene-9: 11-diynoic acid as prisms, m. p 38·4—39·0°, unaltered on further crystallisation (Found: C, 79·0; H, 9·7. Calc. for $C_{18}H_{26}O_2$: C, 78·8; H, 9·6%. Hydrogen no., 58, equiv. to 4·7 double bonds). Light absorption: see Table. The p-*bromophenacyl* ester crystallised from aqueous alcohol in leaflets, m. p. 40·5—41·5° (Found: C, 66·2; H, 6·7. $C_{26}H_{31}O_3Br$ requires C, 66·2; H, 6·6%). The 2-*hydroxyethylamide* crystallised from aqueous acetone in leaflets, m. p. 67·0—68·0° (Found: C, 75·7; H, 10·0. $C_{20}H_{31}O_2N$ requires C, 75·7; H, 9·8%). Light absorption: see Table. The iso*butylamide*, prepared *via* the acid chloride, crystallised from acetone in leaflets, m. p. 52—53° (Found:

C, 80·2; H, 10·9. $C_{22}H_{35}ON$ requires C, 80·2; H, 10·7%). Light absorption: see Table. (iii) A residue of eicosa-9 : 11-diynedioic acid (5·3 g.), m. p., and mixed m. p., 120°.

Distillation of the neutral fraction gave a hydrocarbon (3·2 g.), b. p. 80°/10^{-3} mm., n_D^{25} 1·5530.

Ozonolysis of Octadec-17-ene-9 : 11-diynoic Acid.—A rapid stream of ozonised oxygen was passed for 3 hr. through a solution of synthetic octadec-17-ene-9 : 11-diynoic acid (0·5 g.) in " AnalaR " acetic acid (25 c.c.). Zinc dust (2·0 g.) was then added with cooling and the mixture was steam-distilled into cold water. When 75 c.c. of distillate had been collected, the solution was added to a solution of dimedone (0·55 g.) and sodium acetate (10·6 g.) in water (325 c.c.) and N-hydrochloric acid (75 c.c.), the pH of which had been lowered to 4·6 by the addition of alkali. The buffered solution was kept overnight. The precipitate (195 mg., 36%) was collected and dried. Crystallisation from aqueous methanol gave formaldehyde dimedone derivative, m. p. 189°, undepressed on admixture with an authentic specimen.

Natural Erythrogenic Acid.—The urea complex supplied by Dr. E. M. Meade was treated with water, and the fatty acid thus liberated was isolated by means of ether. Crystallisation from light petroleum (b. p. 60—80°) gave the acid, m. p. 38·5—39·0°, which was characterised (see Table) by formation of the 2-hydroxyethylamide (also supplied by Dr. Meade) and the *p*-bromophenacyl ester (Found: C, 65·8; H, 6·8. Calc. for $C_{26}H_{31}O_3Br$: C, 66·2; H, 6·6%).

Castille states that both permanganate oxidation of the sodium salt of erythrogenic acid (*Annalen*, 1940, **543**, 104), and hydrolysis of the dibromide of the acid (*Bull. Acad. Roy. Méd. Belg.*, 1941, **6**, 152), give " dihydroxyerythrogenic acid," also called " cyanogenic acid," m. p. 92°, by hydroxylation of the terminal double bond. No details of these reactions have been published and the analysis and equivalent weight quoted agree well with a formula $C_{18}H_{32}O_4$ rather than the expected $C_{18}H_{28}O_4$. The homogeneity of the product is therefore doubtful.

*Octyl Toluene-*p*-sulphonate.*—Toluene-*p*-sulphonyl chloride (134 g.) was added rapidly, in one lot, to a cooled (−5°; ice–salt bath) solution of octan-1-ol (83 g.; freshly distilled) in pyridine (400 c.c.; dried and distilled over solid KOH). The mixture was shaken until dissolution was complete, the temperature being kept below 25°. The mixture was kept at −5° for 2 hr. and the temperature then allowed to rise to 20°. Water was added and the product was extracted with chloroform. The extract was washed thoroughly with water, N-sulphuric acid, and again with water, dried (Na_2SO_4), and evaporated at 20° under reduced pressure. Distillation of the residue from a short-path still, and in the presence of solid potassium hydrogen carbonate, gave the *ester* (144 g., 79%), b. p. 170° (bath-temp.)/10^{-4} mm., n_D^{17} 1·4963 (Found: C, 62·8; H, 8·7. $C_{15}H_{24}O_3S$ requires C, 63·3; H, 8·5%).

The ester decomposed on storage, more rapidly on heating, and was stored at 0° over solid potassium hydrogen carbonate.

*Hexyl Toluene-*p*-sulphonate.*—Treatment of hexan-1-ol (82 g.) in pyridine (300 c.c.) with toluene-*p*-sulphonyl chloride (169 g.), as described above, gave the ester (166 g., 80%), b. p. 107° (bath-temp.)/10^{-5} mm., n_D^{25} 1·5005 (Found: C, 61·0; H, 7·9. Calc. for $C_{13}H_{20}O_3S$: C, 60·9; H, 7·9%) [Slotta and Behnisch, *Ber.*, 1933, **66**, 360, give b. p. 145—150° (bath-temp.)/5 × 10^{-2} mm.].

Tetradec-5-yne (cf. Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839; Johnson, Schwarz, and Jacobs, *ibid.*, 1938, **60**, 1882).—Hex-1-yne (11·0 g.) was added to ethylmagnesium bromide (from 3·0 g. of magnesium) in ether (100 c.c.). The mixture was heated under reflux for 2½ hr., then cooled, and added during 1/2 hr. to a solution of octyl toluene-*p*-sulphonate (71 g.) in ether (100 c.c.). The resulting white suspension was heated under reflux overnight. Decomposition with ice and 2N-sulphuric acid, and isolation of the product in the usual manner, gave *tetradec-5-yne* (7·3 g., 34%), b. p. 94°/15 mm., n_D^{20} 1·4460 (Found: C, 85·8; H, 13·8. $C_{14}H_{26}$ requires C, 86·5; H, 13·5%).

Dodec-5-yne.—Repetition of the preceding experiment, but with hexyl toluene-*p*-sulphonate (64 g.), gave *dodec-5-yne* (9·0 g., 44%), b. p. 93°/15 mm., n_D^{23} 1·4397 (Found: C, 86·6; H, 13·1. $C_{12}H_{22}$ requires C, 86·7; H, 13·3%).

2-Methyleicos-1-en-11-yne and 2-Methyleicos-2-en-11-yne.—Reaction of the Grignard complex from the mixture (20·0 g.) of 2-methyldodec-1-en-11-yne and 2-methyldodec-2-en-11-yne with octyl toluene-*p*-sulphonate (64 g.) gave a crude product (15·7 g., 50%), b. p. 122—128°/0·1 mm., which could not be separated by distillation from traces of unchanged octyl ester. The latter were removed by treatment with a boiling solution of ethylmagnesium bromide (from 3·0 g. of magnesium) in ether (100 c.c.). Isolation in the usual way gave the mixture of C_{21} hydrocarbons, b. p. 140°/0·3 mm., n_D^{18} 1·4647 (Found: C, 87·0; H, 13·4. Calc. for $C_{21}H_{38}$: C, 86·8; H, 13·2%).

Purification of the crude product was also effected, though less conveniently, by treatment with alcoholic sodium ethoxide at 20° for 3 hr.

2-Methyloctadec-1-en-11-yne and 2-Methyloctadec-2-en-11-yne.—Reaction of the Grignard complex from the mixture (17·8 g.) of 2-methyldodec-1-en-11-yne and 2-methyldodec-2-en-11-yne with hexyl toluene-*p*-sulphonate (52 g.), and isolation and purification of the product as described in the preceding experiment, gave the mixture of hydrocarbons (6·3 g., 24%), b. p. 118°/0·4 mm., n_D^{23} 1·4648 (Found: C, 86·5; H, 13·1. Calc. for $C_{19}H_{34}$: C, 86·9; H, 13·1%).

Octadec-9-ynoic Acid (*Stearolic Acid*).—A mixture (3·1 g.) of 2-methyleicos-1-en-11-yne and 2-methyleicos-2-en-11-yne in glacial acetic acid (32 c.c.) was oxidised with a solution of chromium trioxide (2·4 g.) in water (2·5 c.c.) in the usual manner. The resulting mixture was diluted with water and extracted with benzene. The extract was washed with water and treated with excess of 2N-sodium hydroxide. The alkaline aqueous layer and the solid sodium salt which separated as a flocculent precipitate were removed and acidified with 2N-sulphuric acid. Isolation of the product with ether and four crystallisations from aqueous alcohol gave stearolic acid (0·63 g., 21%) as prisms, m. p. 46—47°, undepressed on admixture with an authentic specimen, m. p. 46—47° (Adkins and Burks, *Org. Synth.*, 1947, **27**, 76) (Found: C, 77·2; H, 11·7. Calc. for $C_{18}H_{32}O_2$: C, 77·1; H, 11·5%). The p-*bromophenacyl* ester crystallised from aqueous alcohol in plates, m. p. 54° (Found: C, 65·3; H, 8·1. $C_{26}H_{37}O_3Br$ requires C, 65·3; H, 7·8%).

Hexadec-9-ynoic Acid.—Oxidation of a mixture (5·3 g.) of 2-methyloctadec-1-en-11-yne and 2-methyloctadec-2-en-11-yne in glacial acetic acid (55 c.c.) with a solution of chromium trioxide (4·4 g.) in water (5 c.c.), and isolation of the acidic product, gave an oil (3·5 g.) which solidified at 0°. Crystallisation from alcohol and finally from acetic acid yielded the *acid* (0·8 g., 16%) as plates, m. p. 39° (Found: C, 76·4; H, 11·2. $C_{16}H_{28}O_2$ requires C, 76·1; H, 11·2%).

The authors are indebted to the late Dr. H. P. Koch for the infra-red determination. One of them (H. K. B.) thanks the Admiralty and the Ministry of Defence for permission to undertake this work. Analyses and light absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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369. *Polyene Acids. Part VII.* Half Methyl Esters and Amides of the Muconic Acids.*

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The half methyl esters, half amides, and mixed methyl ester amides of the three geometrically isomeric muconic acids have been prepared from the acids by standard methods. Light-absorption characteristics are given. The *cis-cis*- and *cis-trans*-derivatives are inverted to the *trans-trans*-compounds by ultra-violet light and iodine.

The derivatives of *cis-trans*-muconic acid are obtained in positionally isomeric forms, whilst in the *cis-cis*- and the *trans-trans*-series the two terminal positions show the expected equivalence.

Alkoxide ring-fission of the amide (VIII) of γ-carboxymethylbut-α-enolide provides an amide ester of β-ketoadipic acid and not a muconamic acid as would be expected by analogy with the behaviour of the lactonic ester (I).

The three geometrical isomers of muconic acid, and their methyl and diphenylmethyl esters, were described in Part I of this series (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235). Recently we have confirmed the configurations of the acids by semi-hydrogenation experiments (Elvidge, Linstead, and J. F. Smith, *J.*, 1953, 708). We now describe the half methyl esters, half amides, and mixed ester amides of the three muconic acids.

Positional isomerism is encountered in the derivatives of the *cis-trans*-acid, but not in the *cis-cis*- and the *trans-trans*-compounds. Furthermore, the equivalence of the two

* Part VI, *J.*, 1953, 1372.

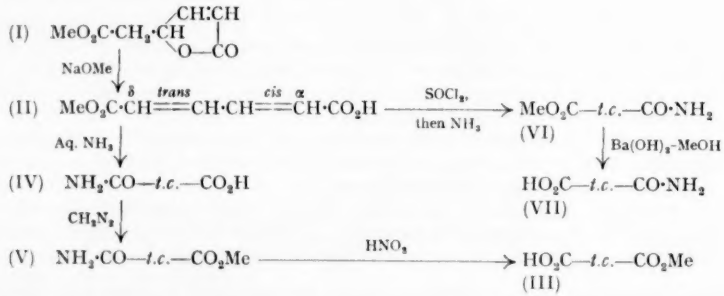
carboxyl groups in *cis-cis*-muconic acid, as well as in the *trans-trans*-acid, has been demonstrated by inversion and positional conversion of derivatives. The *cis-cis*- and *cis-trans*-compounds are easily inverted to the all-*trans*-isomers by ultra-violet light and iodine. These results fully accord with the geometrical configurations already assigned to the muconic acids.

Half Methyl Esters.—Methyl hydrogen *trans-trans*-muconate, m. p. 163°, was prepared in 25% yield by Karrer and Stoll (*Helv. Chim. Acta*, 1931, **14**, 1189) by partial hydrolysis of the diester with methanolic potassium hydroxide.

We attempted similarly to prepare the *cis-cis*-compound from the *cis-cis*-diester but obtained an equimolecular mixture of *cis-cis*-muconic acid and unchanged diester. However, partial esterification was successful, affording methyl hydrogen *cis-cis*-muconate, $C_7H_8O_4$, m. p. 80°, in 34% yield. Its structure was proved by hydrolysis to *cis-cis*-muconic acid and reaction with diazomethane to give methyl *cis-cis*-muconate. On distillation the half ester lactonised to γ-carbomethoxymethylbut-α-enolide (I). Irradiation, in the presence of iodine, inverted the half ester to methyl hydrogen *trans-trans*-muconate, which was hydrolysed to the *trans-trans*-acid. In contrast to *cis-cis*-muconic acid, the *cis-cis*-half ester was not inverted by brief treatment with boiling water or boiling dilute hydrochloric acid.

Application of the partial esterification conditions to *cis-trans*-muconic acid yielded the known methyl hydrogen *trans-cis*-muconate (II),* m. p. 101°, previously obtained (Part I) by methoxide ring-fission of the lactonic ester (I). The structure of (II) follows from that method. Partial hydrolysis of methyl *cis-trans*-muconate, on the other hand, afforded (in poor yield) a new half ester, m. p. 105°, which was therefore the positional isomer (III), methyl hydrogen *cis-trans*-muconate.* The melting point of a mixture of the two *cis-trans*-half esters was strongly depressed. The new half ester (III) with diazomethane gave the known *cis-trans*-dimethyl ester, and on hydrolysis *cis-trans*-muconic acid : hydrogenation and hydrolysis gave adipic acid. In conformity with the assigned configurations, the acid ester (II) lactonised on distillation to γ-carbomethoxymethylbut-α-enolide (I), whereas the acid ester (III) did not, being geometrically unfavourable (cf. Elvidge, Linstead, and Sims, *J.*, 1951, 3386). Each of the half esters (II) and (III) was inverted on irradiation in the presence of iodine to methyl hydrogen *trans-trans*-muconate, and at about the same rate, which was slightly slower than for the *cis-cis*-half ester. The inversions of (II) and (III) to a single *trans-trans*-half ester is a demonstration of the equivalence of the two carboxyl groups in *trans-trans*-muconic acid.

Light-absorption data for the half esters which confirm the open-chain structures are recorded in the Table.



Half Amides and Methyl Ester Amides.—Methyl hydrogen *trans-trans*-muconate with aqueous ammonia gave in good yield *trans-trans*-muconamic acid, m. p. 284°. This has previously been isolated from the urine of rabbits fed with sorbamide (Kuhn, Köhler, and Köhler, *Z. physiol. Chem.*, 1937, **247**, 197). Alkaline hydrolysis of the half amide yielded

* The terms *cis* and *trans* are given in positional order; see *J.*, 1951, 3386. Fully unambiguous names for (II) and (III) are, respectively, (δ)-methyl (α)-hydrogen *cis-trans*-muconate and (α)-methyl (δ)-hydrogen *cis-trans*-muconate.

trans-trans-muconic acid, whilst reaction with diazomethane afforded methyl *trans-trans*-muconamate, m. p. 177°.

cis-cis-Muconamic acid, m. p. 152°, was prepared analogously from the *cis-cis*-half methyl ester and ammonia. Hydrolysis of the half amide with alkali gave *cis-cis*-muconic acid, further characterised as the dimethyl ester, and irradiation in the presence of iodine yielded *trans-trans*-muconamic acid. With diazomethane the *cis-cis*-half amide yielded methyl *cis-cis*-muconamate, m. p. 105°, and an identical product resulted from treatment of methyl hydrogen *cis-cis*-muconate with thionyl chloride (to yield the ester acid chloride) and then ammonia. These syntheses, which produce the same muconamate by conversion of opposite muconic carboxyl groups into amide and ester functions, demonstrate the symmetry of *cis-cis*-muconic acid. Irradiation of the *cis-cis*-muconamate gave the all-*trans*-ester amide.

From the readily available methyl hydrogen *trans-cis*-muconate (II) with ammonia, *cis-trans*-muconic (α)-acid (δ)-amide (IV), m. p. 153°, resulted. This was hydrolysed with hot alkali to *cis-trans*-muconic acid (characterised as the dimethyl ester), and with diazomethane yielded *cis-trans*-muconic (α)-methyl ester (δ)-amide (V), m. p. 116°. Treatment of the latter with nitrous acid afforded methyl hydrogen *cis-trans*-muconate (III), a result which confirmed the geometry of the double bonds as well as the orientation of the ester and amide groupings in (V).

The positionally isomeric half amide ester, *cis-trans*-muconic (α)-amide (δ)-methyl ester (VI), m. p. 114° [depressed by 30° by (V)], was also prepared from methyl hydrogen *trans-cis*-muconate (II) by conversion of this into the ester acid chloride and then reaction with ammonia. Cautious hydrolysis of (VI) with methanolic barium hydroxide provided the second *cis-trans*-half amide, *cis-trans*-muconic (δ)-acid (α)-amide (VII), m. p. 199°. Each of the half amides (IV) and (VII) was inverted, on irradiation, to *trans-trans*-muconamic acid, and each of the ester amides (V) and (VI) similarly gave methyl *trans-trans*-muconamate.

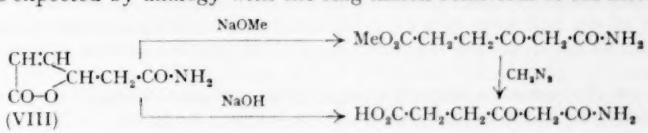
The light-absorption properties of the half amides and their esters, recorded in the Table, agree with the open-chain structures.

Light absorption of muconic derivatives, $R'\cdot CO\cdot CH^{\delta}{:}CH\cdot CH{:}CH^{\alpha}\cdot CO\cdot R$, *in ethanol.*

		cis-cis		*cis*(α*β*)-*trans*(γδ)		*trans-trans*	
R	R'	$\lambda_{max.}$, Å	ε	$\lambda_{max.}$, Å	ε	$\lambda_{max.}$, Å	ε
OMe	OH	2580	20,900	2580	22,400	2570	29,400
		2640 *	19,000	2640	23,700		
OH	OMe			2570 *	24,800		
				2640	25,800		
NH_2	OH	2510	19,000	2510 *	27,500	2510	27,500
		2570	23,100	2570	29,000	2580	31,000
		2640	23,100	2640	29,000	2640	31,000
OH	NH_2			2510 *	18,900		
				2570	21,300		
				2640	21,300		
OMe	NH_2	2510 *	22,300	2490 *	19,400	2510	25,500
		2580	25,900	2570	23,400	2570 *	28,600
		2640	25,900	2640	23,400	2650	30,600
		2780 *	14,700				
NH_2	OMe			2560	22,500		
				2650	26,500		

* Inflection.

In extension of the above work, the action of sodium methoxide on the unsaturated lactonic amide (VIII) was examined, but this reaction did not yield a *cis-trans*-muconic half amide, as expected by analogy with the ring-fission behaviour of the lactonic ester (I).



(VIII)

The lactonic amide (VIII) was best obtained from the corresponding αβ-unsaturated lactonic acid (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228) *via* the acid chloride and mild treatment with ammonia. It was also formed by thermal cyclisation of the geometrically suitable *cis-trans*-muconamic acid (IV). The Δ^{α}-structure of (VIII) was supported by the light absorption (inflection at 2250 Å., $\varepsilon = 3100$). With 1 mol. of sodium methoxide in methanol, (VIII) afforded a neutral ketonic product, isolated as the 2 : 4-dinitrophenylhydrazone, the analysis of which corresponded with that of β-ketoadipic (α)-amide (δ)-methyl ester. Aqueous sodium hydroxide gave the corresponding acid, β-ketoadipic (δ)-acid (α)-amide, also isolated as the 2 : 4-dinitrophenylhydrazone. The latter amide with diazomethane gave the previously encountered neutral derivative.

The double bond in (VIII) is evidently so easily mobile in presence of alkaline reagents that ring-fission yields the enolate ion of a β-ketoadipic derivative even with cold alkoxide. The lactonic acid, γ-carboxymethylbut-α-enolide gave lævulic acid with hot alkali (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*), presumably *via* β-ketoadipic acid and decarboxylation. In the present case the α-carboxyl group of the product is protected (as an amide) and is not therefore eliminated.

Experimental

M. p.s marked * were taken by immersion of the sample in a bath at 165°, with the temperature rising at 10°/min. Other m. p.s were taken normally.

Methyl hydrogen *trans-trans*-muconate had m. p. 163° (Karrer and Stoll, *loc. cit.*).

Methyl Hydrogen cis-cis-*Muconate.*—*cis-cis*-Muconic acid (5 g.) was kept for 48 hr. in the dark with methanol (50 c.c.) containing 0·5% of hydrogen chloride. The solvent was evaporated under reduced pressure, and the portion of the residue soluble in boiling benzene (2 × 25 c.c.) was shaken with aqueous sodium hydrogen carbonate and ether. The aqueous layer was acidified with hydrochloric acid (Congo-red), and the precipitate crystallised from benzene, affording *methyl hydrogen* cis-cis-*muconate* (1·9 g., 34%) as needles, m. p. 80° (Found: C, 53·8; H, 5·3. $C_7H_8O_4$ requires C, 53·9; H, 5·2%.

Hydrogenation of the half ester (220 mg.) in ethanol (5 c.c.) over Adams's catalyst (H_2 uptake at 755 mm./23°: 76·5 c.c. Calc. for 2 double bonds: 70 c.c.) afforded an oil, which was heated under reflux with concentrated hydrochloric acid (2 c.c.). Evaporation of the hydrolysate gave adipic acid (155 mg.), m. p. and mixed m. p. 146—148°.

Methyl hydrogen *cis-cis*-muconate (100 mg.) was dissolved in 10% aqueous sodium hydroxide (1 c.c.), and after 30 min. the solution was acidified. From ethanol, the precipitate (50 mg.) formed prisms, m. p. 185—187° * undepressed by *cis-cis*-muconic acid.

The *cis-cis*-half ester (50 mg.) was treated with an excess of ethereal diazomethane. The product, isolated by evaporation of the solution, was crystallised from aqueous methanol, affording needles, m. p. 73—73·5° undepressed by methyl *cis-cis*-muconate, but depressed to 50—55° by the *cis-trans*-dimethyl ester.

Distillation of methyl hydrogen *cis-cis*-muconate (2 g.) (bath-temp., 190°) afforded γ-carbomethoxymethylbut-α-enolide (I) (0·85 g., 42%), b. p. 155°/12 mm., n_D^{18} 1·4743, and a residue of a neutral, brittle resin.

After being heated in boiling water (1 c.c.) for 2 min., methyl hydrogen *cis-cis*-muconate (100 mg.) was recovered (90 mg.), m. p. and mixed m. p. 79°, and was unchanged by similar treatment with boiling 2N-hydrochloric acid.

Methyl hydrogen *cis-cis*-muconate (0·2 g.) in benzene (2 c.c.), containing a trace of iodine, was irradiated with ultra-violet light from a Hanovia lamp for 15 min. Recrystallisation of the precipitate (yield, almost quantitative) from benzene gave needles, m. p. 163°, of methyl hydrogen *trans-trans*-muconate.

(δ)-*Methyl* (α)-*Hydrogen* cis-trans-*Muconate* (II).—This, m. p. 101°, was prepared by Elvidge, Linstead, Sims, and Orkin (*loc. cit.*) from (I), and was also obtained by treating *cis-trans*-muconic acid (10 g.) with methanol (150 c.c.) containing 0·5% of hydrogen chloride for 16 hr. (cf. *cis-cis* case, above) [yield, 5·2 g. (47%); m. p. 90—95°, raised to 99—100° (undepressed by the previous sample) by crystallisation 3 times from benzene].

Distillation of the half ester (1·8 g.) (bath-temp. 190°) gave γ-carbomethoxymethylbut-α-enolide (0·65 g., 36%), b. p. 154°/11 mm., n_D^{15} 1·4738, together with a residue of a neutral, brittle resin.

(α)-*Methyl* (δ)-*Hydrogen* cis-trans-*Muconate* (III).—Methyl *cis-trans*-muconate (3 g.) in methanol (10 c.c.) was added to methanolic barium hydroxide (22 c.c.; 0·79N). Next day, the

precipitate was washed with methanol (10 c.c.), and its solution in water (20 c.c.) acidified. Isolation with ether (3 × 25 c.c.) yielded an oil, which was taken up in hot benzene (25 c.c.). (α)-*Methyl* (δ)-*hydrogen* cis-trans-*muconate* (220 mg., 8·3%) separated from benzene as needles, m. p. 105—106° (Found: C, 53·7; H, 5·3%; equiv., 156·2. $C_7H_8O_4$ requires C, 53·9; H, 5·2%; equiv., 156·1). A mixture with (δ)-methyl (α)-hydrogen *cis-trans*-muconate (II) (m. p. 101°) had m. p. 80—85°.

Hydrogenation of the *cis-trans*-half ester (III) (200 mg.) in ethanol (5 c.c.) over Adams's catalyst (30 mg.) (H_2 uptake at 755 mm./23°: 69 c.c. Calc. for 2 double bonds: 63 c.c.) and hydrolysis of the oily product with boiling concentrated hydrochloric acid (2 c.c.) for 30 min. yielded adipic acid (130 mg.), m. p. 147—149° and mixed m. p. 148—149°.

The *cis-trans*-half ester (III) with diazomethane in ether gave methyl *cis-trans*-muconate, which crystallised from aqueous methanol as needles, m. p. and mixed m. p. 73—74°. The m. p. of a mixture with methyl *cis-cis*-muconate was depressed to 60—65°.

The half ester (III) (120 mg.) was kept for 1 hr. with 10% sodium hydroxide (2 c.c.). On acidification, *cis-trans*-muconic acid was precipitated (70 mg., 82%), m. p. 180—184°* and mixed m. p. 181—185°.* The product, with diazomethane, gave methyl *cis-trans*-muconate as needles, m. p. and mixed m. p. 74—75°.

When heated at 190°/11 mm., the half ester (III) failed to distil but in part sublimed. The sublimate (30 mg.) had m. p. 105° undepressed by the starting material. The residue was a neutral, brown resin.

Comparison of the Rates of Inversion of the cis-*Half Esters.*—100-Mg. samples of the esters in benzene (3-c.c. portions) containing a trace of iodine were simultaneously irradiated with light from a 100-w filament lamp, and the times (in min.) for appearance of a precipitate noted: methyl hydrogen *cis-cis*-muconate, 7; (III), 8; (II), 8. In each case the precipitate had m. p. 163° alone and when mixed with methyl hydrogen *trans-trans*-muconate.

trans-trans-*Muconamic Acid.*—Methyl hydrogen *trans-trans*-muconate (100 mg.) was kept with aqueous ammonia (3 c.c.; *d* 0·88) for 4 days, and the solution then acidified. The precipitated *trans-trans*-muconamic acid (80 mg., 88%) crystallised from water as needles, m. p. 284—285° (decomp.) (Found: C, 51·0; H, 4·9; N, 9·7. Calc. for $C_6H_7O_3N$: C, 51·1; H, 5·0; N, 9·9%). Kuhn, Köhler, and Köhler (*loc. cit.*) record m. p. 281—282°.

Hydrolysis of the *trans-trans*-half amide (100 mg.) with boiling 10% aqueous sodium hydroxide (1·5 c.c.) for 1 hr., and acidification, yielded *trans-trans*-muconic acid (80 mg., 80%), m. p. and mixed m. p. 298—300° (decomp.).

Methyl trans-trans-*muconamate*, obtained in high yield from the muconamic acid and diazomethane, crystallised from benzene as needles, m. p. 177—178° (Found: N, 9·3. $C_7H_9O_3N$ requires N, 9·0%).

cis-cis-*Muconamic Acid.*—Prepared analogously to the all-*trans*-compound, cis-cis-*muconamic acid* (48% yield) crystallised from ethanol–light petroleum (b. p. 40—60°) as needles, m. p. 152—153° (Found: C, 51·35; H, 5·0; N, 9·9. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

Hydrolysis of the *cis-cis*-half amide (100 mg.) (as for the all-*trans*-isomer) gave *cis-cis*-muconic acid (80 mg.), m. p. 185—187°*, converted by diazomethane into methyl *cis-cis*-muconate, m. p. 73°, undepressed by authentic material, but depressed to 53—58° by methyl *cis-trans*-muconate.

Irradiation of the *cis-cis*-half amide (100 mg.), in ethanol (5 c.c.) containing a trace of iodine with light from a 100-w filament lamp for 30 min., gave a precipitate of *trans-trans*-muconamic acid, which crystallised from water as needles (85 mg., 85%), m. p. and mixed m. p. 285—286° (decomp.).

Methyl cis-cis-*muconamate*, from *cis-cis*-muconamic acid and ethereal diazomethane, crystallised from benzene as needles (yield 60%), m. p. 104—105° (Found: C, 54·4; H, 5·9; N, 8·9; $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%). In an alternative preparation, methyl hydrogen *cis-cis*-muconate (400 mg.) was heated under reflux with thionyl chloride (5 c.c.) for 15 min. Excess of the reagent was removed under reduced pressure, and the product added slowly to aqueous ammonia (2 c.c.; *d* 0·88) cooled in ice. Crystallisation of the product from benzene afforded fine needles, m. p. 105° undepressed by the preceding preparation.

Irradiation under the previous conditions gave methyl *trans-trans*-muconamate (75%), m. p. and mixed m. p. 176—177°.

cis-trans-*Muconic* (α)-*Acid* (δ)-*Amide* (IV).—(δ)-Methyl (α)-hydrogen *cis-trans*-muconate (II) (0·4 g.) was kept with aqueous ammonia (5 c.c.; *d* 0·88) for 4 days. The solution was concentrated under reduced pressure and acidified, and the precipitate was crystallised from hot water. cis-trans-*Muconic* (α)-*acid* (δ)-*amide* (0·28 g., 77%) formed needles, m. p. 152—153° (Found:

C, 51·2; H, 5·2; N, 9·65. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). The m. p. was depressed to 143—145° by *cis-cis*-muconamic acid (m. p. 152—153°).

Hydrolysis of (IV) with alkali (as in previous cases) for 60 min. produced *cis-trans*-muconic acid (55%), m. p. and mixed m. p. 184—186°,* which with diazomethane gave methyl *cis-trans*-muconate, m. p. and mixed m. p. 73—74°, depressed to 52—56° by methyl *cis-cis*-muconate.

cis-trans-*Muconic* (α)-*Methyl Ester* (δ)-*Amide* (V)—Obtained from the *cis-trans*-muconamic acid (IV) with diazomethane, this *compound* crystallised from benzene as needles, m. p. 116° (Found: C, 54·3; H, 5·95; N, 9·4. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%), depressed to 75—82° by methyl *cis-cis*-muconamate.

A suspension of this (α)-methyl ester (δ)-amide (200 mg.) in 2N-hydrochloric acid (10 c.c.) was treated at room temperature with 10% aqueous sodium nitrite (2 c.c.), and after 5 hr. the solution was extracted with ether (3 × 10 c.c.). Evaporation of the extract gave (α)-methyl (δ)-hydrogen *cis-trans*-muconate (45 mg., 22%), which crystallised from water as needles, m. p. 103—104° and mixed m. p. 104—105°.

cis-trans-*Muconic* (α)-*Amide* (δ)-*Methyl Ester* (VI).—(δ)-Methyl (α)-hydrogen *cis-trans*-muconate (0·5 g.) was heated under reflux with thionyl chloride (10 c.c.) for 10 min. Excess of reagent was distilled off under reduced pressure and the residue added slowly to aqueous ammonia (2 c.c.; *d* 0·88) at 0°. From benzene, cis-trans-*muconic* (α)-*amide* (δ)-*methyl ester* (0·39 g., 77%) separated as fine needles, m. p. 114—115° (Found: C, 54·1; H, 5·8; N, 8·9. $C_7H_9O_3N$ requires C, 54·2; H, 5·85; N, 9·0%), depressed to 74—80° by methyl *cis-cis*-muconamate.

cis-trans-*Muconic* (α)-*Amide* (δ)-*Acid* (VII).—The amide ester (VI) (0·1 g.) was dissolved in methanolic barium hydroxide (1 c.c.; 0·8N). After 30 min., the solution was diluted with water (1 c.c.), acidified, and kept at 0° for several hr. The cis-trans-*muconic* (α)-*amide* (δ)-*acid* (58 mg., 63%), which separated crystallised from water as needles, m. p. 199—200° (decomp.) (Found: C, 51·3; H, 5·4; N, 10·0. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

Inversion of the cis-trans-*Muconic Amides.*—Solutions of the *cis-trans*-amides, containing traces of iodine, were irradiated with light from a 100-w filament lamp, and the precipitates recrystallised, and identified by mixed m. p.s.

Compound	Solvent	Time (min.)	Product (all-*trans*)	Solvent for recrystn. and yield (%)	M. p.
(IV) (0·1 g.)	H_2O (5 c.c.)	15	Muconamic acid	H_2O, 90	284—285° (decomp.)
(VII) (0·2 g.)	EtOH (30 c.c.)	60	,, ,,	,, 95	285—286 (decomp.)
(V) (0·1 g.)	C_6H_6 (10 c.c.)	20	Methyl muconamate	C_6H_6, 85	177—178
(VI) (50 mg.)	,, (2 c.c.)	60	,, ,,	,, 70	,,

Amide of γ-*Carboxymethylbut-*α-*enolide* (VIII).—(*a*) γ-Carboxymethylbut-α-enolide (*J.*, 1950, 2228) (1 g.) was heated under reflux with thionyl chloride (10 c.c.) for 15 min. Excess of reagent was removed under reduced pressure and the residue added slowly to aqueous ammonia (2 c.c.; *d* 0·88) at 0°. From ethanol the *amide* of γ-carboxymethylbut-α-enolide (0·25 g.) crystallised as needles, m. p. 146—147° (Found: C, 50·9; H, 4·9; N, 10·2. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%). Light absorption in ethanol: inflection at 2250 Å, ε = 3100.

(*b*) *cis-trans*-Muconic (α)-acid (δ)-amide (180 mg.) was kept at 155—165° for 2 hr., and the red melt was cooled and extracted with saturated aqueous sodium hydrogen carbonate (2 c.c.). Crystallisation of the residue from ethanol afforded needles (30 mg., 16%), m. p. 145—146°, and mixed m. p. 146—147° with the preparation (*a*). The m. p. of a mixture with the starting material (m. p. 152—153°) was depressed to 137—142°.

Reaction of (VIII) *with Sodium Methoxide.*—The lactonic amide (220 mg.) in methanol (5 c.c.) was kept with methanolic sodium methoxide (0·8 c.c.; 2·4N) for 20 min. The solution was then evaporated to small bulk under reduced pressure, diluted with water (2 c.c.), acidified with hydrochloric acid, and treated with aqueous 2:4-dinitrophenylhydrazine hydrochloride. After several days at 0°, the neutral precipitate (280 mg., 50%) was crystallised from aqueous ethanol, affording β-*ketoadipic* (α)-*amide* (δ)-*methyl ester* 2:4-*dinitrophenylhydrazone* as yellow needles, m. p. 169—170° (Found: C, 43·65; H, 4·4; N, 19·6. $C_{13}H_{15}O_7N_5$ requires C, 44·2; H, 4·3; N, 19·8%).

Reaction of (VIII) *with Sodium Hydroxide.*—The lactonic amide (200 mg.) was dissolved in 10% aqueous sodium hydroxide (2 c.c.), and after 20 min. the solution was acidified and kept at 0° with aqueous 2:4-dinitrophenylhydrazine hydrochloride. β-*Ketoadipic* (δ)-*acid* (α)-

amide 2 : 4-*dinitrophenylhydrazone* (310 mg., 72%) crystallised from aqueous ethanol as yellow needles, m. p. 191—192° (decomp.) (Found : C, 42·5; H, 3·95; N, 20·6. $C_{12}H_{13}O_7N_5$ requires C, 42·5; H, 3·9; N, 20·6%).

Treatment of a suspension of the acid derivative (200 mg.) in ether with diazomethane afforded the ester derivative (yield, almost theoretical), m. p. and mixed m. p. 167—169°.

Analyses were performed in the microanalytical laboratory (Mr. F. H. Oliver) and measurements of light absorption in the spectrographic laboratory (Mrs. A. I. Boston) of this Department. Grateful acknowledgment is made to the Ministry of Education for a grant (to P. S.).

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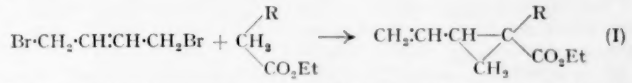
370. cyclo*Propanes*. *Part III*.* *The Condensation of 1 : 4-Dibromobut-2-ene with Ethyl Cyano- and Aceto-acetate.*

By R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon.

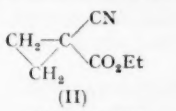
The main products from the condensation of *trans*-1 : 4-dibromobut-2-ene with ethyl sodiocyanoacetate and sodioacetoacetate are ethyl 1-cyano- and 1-aceto-2-vinyl*cyclo*propane-1-carboxylate respectively. From the former reaction a mixture of ethyl 3-cyano-2-imino-4- and -5-vinyl*cyclo*pentane-1-carboxylate is also obtained.

We recently reported (Part I, *J*., 1952, 3610) that *trans*-1 : 4-dibromobut-2-ene reacts with ethyl sodiomalonate to give ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (I; R = CO_2Et) in good yield :



This new route to vinyl*cyclo*propanes has now been further exemplified by carrying out analogous reactions with ethyl cyanoacetate and acetoacetate.

When 1 : 4-dibromobut-2-ene was condensed with ethyl cyanoacetate two products were obtained. One, isolated in yields up to 40%, was shown to be the substituted *cyclo*propane (I; R = CN). On ozonolysis, followed by oxidative fission of the ozonide and hydrolysis of the resulting nitrile, *cyclo*propane-1 : 1 : 2-tricarboxylic acid was obtained in 24% overall yield and identified by direct comparison with an authentic specimen. Hydrolysis of the ester (I; R = CN) gave the corresponding cyano-acid, which melted over a wide range and was obviously a mixture of *cis*- and *trans*-isomers.



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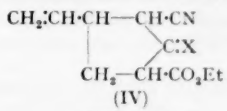

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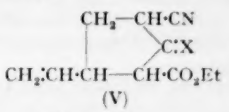

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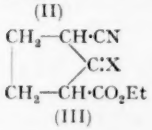

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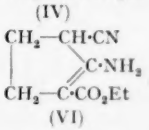

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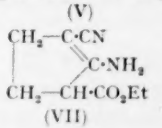


(VII)

Best and Thorpe (*J*., 1909, **95**, 685) showed that the cyano-ester (II) reacts with ethyl cyanoacetate, in the presence of small amounts of the sodio-derivative of the latter, to give the imino-*cyclo*pentane (III; X = NH). It seemed probable that, under the conditions employed for the condensation of dibromobutene with ethyl cyanoacetate, the substituted *cyclo*propane (I; R = CN) formed initially would, to some extent, react further with ethyl cyanoacetate to give vinyl derivatives of (III; X = NH). The second product from the condensation was therefore regarded as a mixture of (IV; X = NH)

* Part II, *J*., 1952, 3316.

and (V; X = NH). When this was kept, one of the isomers separated as a crystalline solid. Acid hydrolysis of the mixture gave the corresponding β-keto-esters (IV; X = O) and (V; X = O) in which the presence of a terminal double bond was demonstrated by ozonolysis to formaldehyde (29%). Catalytic reduction of the keto-esters yielded the dihydro-derivatives, which on hydrolysis and decarboxylation were converted into the known 3-ethyl*cyclo*pentanone (Part II), thereby confirming the structures assigned to the isomers in the second fraction from the dibromobutene condensation.

Spectral data (Table 1) for the imino-compounds (III—V; X = NH) indicate that they exist, at least in solution, largely in the amino-forms, *e.g.*, (VI) and/or (VII). The light-absorption properties of the mixture of β-keto-esters (IV; X = O) and (V; X = O), and of their dihydro-derivatives, are in good agreement with those of ethyl 3-cyano-2-keto*cyclo*pentane-1-carboxylate (III; X = O) (Table 2). The maxima recorded with alcoholic solutions must be due to the enolic forms of the keto-esters; the shifts to longer wave-lengths observed with alkaline media result from the conversion of the enols into the corresponding enolates.

TABLE 1.

	$\lambda_{max.}$, Å *	ε	$\lambda_{max.}$, Å *	ε
(IV; X = NH) and (V; X = NH)	2710	17,000	2760 †	16,000
(IV; X = NH) or (V; X = NH)	2690	11,500	2790	10,000
(III; X = NH)	2690	14,000	2800	15,000

* In chloroform. † Inflexion.

TABLE 2.

	In alcohol. $\lambda_{max.}$, Å	ε	In 2% aqueous KOH. $\lambda_{max.}$, Å	ε		In alcohol. $\lambda_{max.}$, Å	ε	In 2% aqueous KOH. $\lambda_{max.}$, Å	ε
(IV; X = O) and (V; X = O)	2280	8500	2270	3,500	(III; X = O) †	2270	6500	2580 *	12,000
	2370		2680	12,500		2360	6000	2690	13,000
	2420		2760 *	10,500		2510 *	5000	2790 *	11,000
Dihydro-derivatives of (IV; X = O) and (V; X = O)	2360	8000	2580 *	12,500					
	2410		2680	13,000					
			2740 *	12,500					

* Inflexion.
† Prepared from (III; X = NH) by Best and Thorpe's method (*J.*, 1909, **95**, 685).

TABLE 3.

	$\lambda_{max.}$, Å	ε
CH_2:CH·CH(COMe)·C(CO_2Et)CH_2	2510	1,150
	2570	
	2640	
CH_2:CH·C:C·COMe [1]	2510	8,500
	2580 *	8,000
CH_2:CH·CH:CH·CHO [2]	2580	29,000

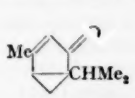
	$\lambda_{max.}$, Å	ε
CHMe:CH·CH:CH·COMe [3] ...	2700	28,500
Umbellulone (VIII) [4]	2200	5,000
	2650	2,900
Piperitone (IX) [4]	2355	17,780
Carone (X) [4]	<2200	>2,680

* Inflexion.
[1] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39. [2] Bader, Weedon, and Woods, *J.*, 1951, 3009. [3] Heilbron, Jones, and Richardson, *J.*, 1949, 287. [4] Gillam and West, *J.*, 1945, 95.

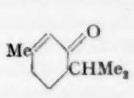
The main product (52%) from the reaction of 1 : 4-dibromobut-2-ene with ethyl sodioacetoacetate was the substituted *cyclo*propane (I; R = COMe). Its structure was established by ozonolysis, followed by hypobromite oxidation and hydrolysis, whereupon *cyclo*propane-1 : 1 : 2-tricarboxylic acid was obtained in 32% overall yield. Catalytic hydrogenation of (I; R = COMe) over platinum at 20° resulted in the rapid absorption of 1·9 mol. of hydrogen, thus affording a further example of the ready reductive fission of a vinyl*cyclo*propane (cf. Part I). Hydrolysis of the saturated keto-ester and decarboxylation yielded methyl pentyl ketone.

The ultra-violet light absorption spectrum of (I; R = COMe), unlike that of (I; R = CO_2Et) or (I; R = CN), exhibits maxima in the 2500—2650 Å region (Table 3). These absorption bands are similar in position to, but of much lower intensity than, those of vinylacetylenic and butadienyl ketones, suggesting that in (I; R = COMe) there is some

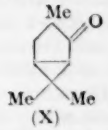
electronic interaction between the *cyclo*propane ring, the double bond, and the carbonyl group. It has been shown (Part I), by molecular-refractivity measurements, that conjugation in (I; R = CO_2Et) is confined almost exclusively to the vinyl*cyclo*propane system. This difference is in accord with the observations of others on the relative abilities of the



(VIII)



(IX)



(X)

*cyclo*propane ring to conjugate with carbonyl and ester groups (for references see Part I). Mutual interaction of the three chromophores under consideration has been noted previously (Gillam and West, *J.*, 1945, 95) in umbellulone (VIII), which has light absorption properties different from those of other αβ-unsaturated ketones, such as piperitone (IX), and of carone (X) (Table 3).

In addition to (I; R = COMe) small amounts of two other products were isolated from the condensation of dibromobutene with ethyl sodioacetoacetate. These have not been examined, but it is probable that one, $C_{16}H_{24}O_6$, was formed by replacement of both bromine atoms in dibromobutene by acetoacetate residues, and the other, $C_{12}H_{20}O_4$, by substitution of the first bromine by acetoacetate and the second by an ethoxyl group. Products of solvolysis have not previously been encountered in the reaction of dibromobutene with active methylene compounds.

Experimental

The 1 : 4-dibromobut-2-ene used was the crystalline, *trans*-isomer, m. p. 54°.

Condensation of 1 : 4-*Dibromobut-2-ene with Ethyl Sodiocyanoacetate*.—A warm solution of dibromobutene (53·5 g.) in alcohol (200 c.c.) was added during ½ hr. to a well-stirred, warm suspension of ethyl sodiocyanoacetate (from 56·5 g. of ethyl cyanoacetate and 11·5 g. of sodium) in alcohol (200 c.c.). The mixture was heated under reflux until neutral to litmus (2 hr.), then cooled and filtered. The filtrate was evaporated under reduced pressure, and the residue poured into water. Isolation of the product with ether and distillation gave: (i) *Ethyl* 1-*cyano*-2-*vinyl*cyclo*propane*-1-*carboxylate* (4·4 g., 10%), b. p. 112°/11 mm., n_D^{24} 1·4650 (Found: C, 65·3; H, 6·95. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7%). It showed no light absorption of $E^{1\%}_{1\,cm.}$ >10 at wave-lengths >2220 Å. (ii) A mixture (16·8 g., 30%) of ethyl 3-cyano-2-imino-4- and -5-vinyl*cyclo*pentane-1-carboxylate, b. p. 107°/0·15 mm., n_D^{24} 1·5242 (Found: C, 63·7; H, 6·85%). After 1—2 hr., an alcoholic solution of the mixture gave a violet colour with ferric chloride, probably owing to hydrolysis of the imino-group. On storage at 0° the mixture partly crystallised. The solid was separated and crystallised from benzene–light petroleum (b. p. 40—60°), giving one of the isomeric *esters* (*ca.* 30% of the mixture) as plates, m. p. 86·5—88° (Found: C, 64·25; H, 7·05. $C_{11}H_{14}O_2N_2$ requires C, 64·05; H, 6·85%).

In another experiment, the suspension of ethyl sodiocyanoacetate was added during 1 hr. to a boiling solution of dibromobutene, and the resulting mixture heated under reflux for a further hr. Isolation of the product as described above gave the *cyclo*propane derivative in 40% yield.

cyclo*Propane*-1 : 1 : 2-*tricarboxylic Acid*.—A stream of ozonised oxygen (*ca.* 3% of O_3) was bubbled through a cooled solution of ethyl 1-cyano-2-vinyl*cyclo*propane-1-carboxylate (1·0 g.) in acetic acid ("AnalaR"; 12 c.c.) for 7 hr. Hydrogen peroxide (30 c.c.; 20-vol.) was then added, and the mixture kept at 20° overnight. The resulting solution was evaporated under reduced pressure. The residue (2 c.c.) was heated under reflux with a solution of potassium hydroxide (3·2 g.) in water (3 c.c.) and alcohol (2 c.c.) until the evolution of ammonia ceased (21 hr.). The solution was acidified and extracted thoroughly with ether (constant extractor overnight). Evaporation of the ethereal extract yielded a solid (857 mg.), m. p. 155—157° (decomp.), which was crystallised twice from ether and gave *cyclo*propane-1 : 1 : 2-tricarboxylic acid (250 mg.), m. p. 183° (decomp.), undepressed on admixture with an authentic specimen (Conrad and Gutzeit, *Ber.*, 1884, **17**, 1185, give m. p. 184°, decomp.).

1-*Cyano*-2-*vinyl*cyclo*propane*-1-*carboxylic Acid*.—Ethyl 1-cyano-2-vinyl*cyclo*propane-1-carboxylate (9·0 g.) was shaken for 2 hr. with potassium hydroxide (3·6 g.) in water (10 c.c.). The resulting homogeneous solution was extracted with ether and then acidified with dilute (1 : 5) sulphuric acid. The solution was saturated with ammonium sulphate, and the product isolated by

thorough extraction with ether. Evaporation of the extract gave the acid (7·2 g.) as a mixture of isomers which crystallised from benzene–light petroleum (b. p. 40—60°) in prisms, m. p. 67—79° (Found : C, 61·45; H, 5·05%; equiv., 137. Calc. for $C_7H_7O_2N$: C, 61·3; H, 5·15%; equiv., 137). The acid was not decarboxylated when heated to 200°.

Ethyl 3-*Cyano*-2-*keto*-4- *and* -5-*vinyl*cyclo*pentane*-1-*carboxylate* (cf. Best and Thorpe, *loc. cit.*).—A solution of ethyl 3-cyano-2-imino-4- and -5-vinyl*cyclo*pentane-1-carboxylate (7·3 g.) in concentrated hydrochloric acid (40 c.c.) was kept for 5 min. and then diluted with an equal volume of water and extracted with ether. The ethereal solution was extracted three times with aqueous sodium carbonate (5% w/v). The carbonate extracts were combined and acidified with concentrated hydrochloric acid. Isolation of the oil thus liberated with ether gave the mixture of ketones (5·8 g., 80%), b. p. 123°/0·15 mm., n_D^{24} 1·4755, which gave an intense wine-red colour with ferric chloride but did not react with Brady's reagent (Found : C, 63·95; H, 6·3. Calc. for $C_{11}H_{13}O_3N$: C, 63·75; H, 6·3%).

Ozonolysis. A slow stream of ozonised oxygen was bubbled through a cooled solution of the ketones (500 mg.) in acetic acid (" AnalaR "; 10 c.c.) for 2½ hr. Zinc dust (1·0 g.) was added, and the mixture steam-distilled in an atmosphere of nitrogen. The distillate was treated with an excess of dimedone reagent and yielded the derivative of formaldehyde (204 mg., 29%) as needles, m. p. 185—189°, raised by crystallisation from aqueous methanol to 188—189°, undepressed on admixture with an authentic specimen, m. p. 189°.

Ethyl 3-*Cyano*-2-*keto*-4- *and* -5-*ethyl*cyclo*pentane*-1-*carboxylate*.—A solution of the preceding isomeric ketones (3·1 g.) in alcohol (25 c.c.) was shaken in hydrogen in the presence of Adams's catalyst. When the rate of absorption became very small, the reaction was interrupted (hydrogen absorbed : 401 c.c. at 23°/741 mm. Calc. for 1 mol., 373 c.c.). Removal of catalyst and solvent, and distillation of the residue, gave the dihydro-derivatives (1·4 g., 44%), b. p. 123°/0·5 mm., n_D^{22} 1·4633, which gave an intense wine-red colour with ferric chloride (Found : C, 62·7; H, 7·5. Calc. for $C_{11}H_{15}O_3N$: C, 63·15; H, 7·25%).

3-*Ethyl*cyclo*pentanone*.—A solution of ethyl 3-cyano-2-keto-4- and -5-ethyl*cyclo*pentane-1-carboxylate (0·65 g.) in concentrated sulphuric acid (1·3 g.) was kept at 20° for 2½ hr. and then diluted with water (6 c.c.). The mixture was heated under reflux for 6 hr. and then kept overnight. Steam-distillation and isolation of the product from the distillate by ether-extraction gave 3-ethyl*cyclo*pentanone (0·3 g.). The 2 : 4-dinitrophenylhydrazone crystallised from methanol in plates, m. p. 78°, undepressed on admixture with the specimen described in Part II (*J.*, 1952, 3616). The di-*m*-nitrobenzylidene derivative crystallised from alcohol–ethyl acetate in needles, m. p. 155—156°, undepressed on admixture with the specimen described in Part II.

Ethyl 1-*Acetyl*-2-*vinyl*cyclo*propane*-1-*carboxylate*.—A solution of ethyl sodioacetoacetate (from 65 g. of ethyl acetoacetate and 11·5 g. of sodium) in alcohol (190 c.c.) was added during 1 hr. to a boiling solution of 1 : 4-dibromobut-2-ene (53·5 g.) in alcohol (200 c.c.). The mixture was stirred at 20° overnight and then poured into water. Isolation of the product with ether and distillation gave : (i) *Ethyl* 1-*acetyl*-2-*vinyl*cyclo*propane*-1-*carboxylate* (23·6 g.), b. p. 97°/12 mm., n_D^{19} 1·4630 (Found : C, 65·7; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%. Hydrogen no. : 91·1, equiv. to 2·0 double bonds). It gave no colour with ferric chloride. Light absorption : see Table 3. (ii) A colourless mobile liquid (4·8 g.; 8%), b. p. 103°/0·4 mm., n_D^{24} 1·4471, which gave a blue colour with ferric chloride [Found : C, 63·0; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·8%. Hydrogen no. (Adams's catalyst; acetic acid), 119, equiv. to 1·9 double bonds]. (iii) A viscous oil (1·8 g.; 2·3%), b. p. 150° (bath-temp.)/10^{-5} mm., n_D^{22} 1·4621, which gave a blue colour with ferric chloride (Found : C, 61·6; H, 7·75. $C_{16}H_{24}O_6$ requires C, 61·5; H, 7·75%).

cyclo*Propane*-1 : 1 : 2-*tricarboxylic Acid*.—A slow stream of ozonised oxygen (*ca.* 3% of O_3) was bubbled through a cooled solution of ethyl 1-aceto-2-vinyl*cyclo*propane-1-carboxylate (1·5 g.) in acetic acid (" AnalaR "; 12 c.c.) for 6 hr. Hydrogen peroxide (35 c.c.; 20-vol.) was added, and the solution kept at 20° overnight and then evaporated under reduced pressure. The residue (*ca.* 2 c.c.) was made slightly basic by addition of dilute alkali and cooled to 0°. A solution of sodium hypobromite (from 9·0 g. of sodium hydroxide and 4 c.c. of bromine in 40 c.c. of water) was added slowly, and the mixture kept at 20° for 1 hr. The mixture was extracted with ether and then acidified with concentrated hydrochloric acid. The excess of hypobromite was decomposed by addition of sodium hydrogen sulphite, and the resulting solution was extracted thoroughly with ether (constant ether-extractor, overnight). Evaporation of the extract yielded a solid (630 mg.) which, crystallised twice from ether, gave *cyclo*propane-1 : 1 : 2-tricarboxylic acid (460 mg.), m. p. 184° (decomp.), undepressed on admixture with an authentic specimen.

Methyl Pentyl Ketone.—A solution of ethyl 1-acetyl-2-vinyl*cyclo*propane-1-carboxylate (2·19 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (532 c.c. at 28°/765 mm., equiv. to 1·85 double bonds). The catalyst and solvent were removed and the residue was shaken with aqueous sodium hydroxide (20 c.c., 5% w/v) for 7 hr. at 20°. The mixture was extracted with ether, and the aqueous layer acidified with sulphuric acid (2 c.c.; 50% v/v) and steam-distilled. The distillate was saturated with potassium carbonate and extracted with ether. Distillation of the extract gave methyl pentyl ketone (0·66 g.), b. p. 142°. The 2 : 4-dinitrophenylhydrazone was purified by chromatographic adsorption on alumina from benzene solution and crystallisation from methanol; it had m. p. 72—73°, undepressed on admixture with an authentic specimen.

The investigations described in this and the following paper were performed during the tenure by one of us (R. W. K.) of a Beaverbrook Overseas Scholarship. Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mr. A. I. Boston) laboratories of this Department.

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371. cyclo*Propanes*. *Part IV*.* *A New Route to Some* bicyclo[3 : 1 : 0]*Hexene Derivatives*.

By R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon.

Condensation of *cis*- and *trans*-1 : 4-dibromo*cyclo*pent-2-ene with ethyl sodiomalonate gives ethyl *bicyclo*[3 : 1 : 0]hex-2-ene-6 : 6-dicarboxylate (I; R = R′ = Et) in 17 and 33% yield respectively. In elucidating the structure of this compound, in which one ester group is sterically hindered, a number of transformations have been effected. Further examples of ready reductive fission of a *cyclo*propane ring are recorded.

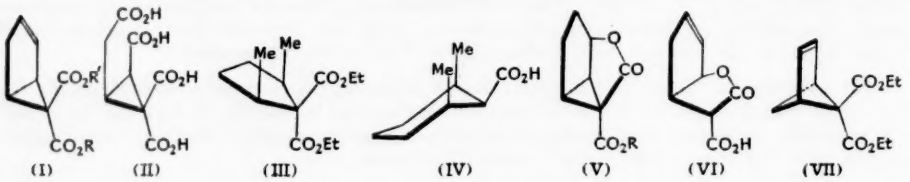
Hitherto only 1 : 4-dibromobut-2-ene has been used as starting material in the route to vinyl*cyclo*propane derivatives described in previous papers in this series. It was of obvious interest to extend the reaction, if possible, to dibromo-*cyclo*pentenes and -*cyclo*hexenes as a new synthesis of the *bicyclo*[3 : 1 : 0]hexane and *bicyclo*[4 : 1 : 0]heptane ring systems present in compounds of the thujane and carane type respectively. With this aim, the condensation of 1 : 4-dibromo*cyclo*pent-2-ene with ethyl malonate has now been studied.

From the reaction of the *trans*-dibromo*cyclo*pentene with ethyl sodiomalonate a dicarboxylic ester, $C_{12}H_{16}O_4$, was obtained in 33% yield. This did not exhibit the characteristic ultra-violet light absorption of a *cyclo*pentadiene and was formulated as (I, R = R′ = Et) by analogy with the corresponding product from dibromobutene (Part I; *J.*, 1952, 3610). Ozonolysis of the diester, followed by oxidative fission of the ozonide and hydrolysis, led to a tetracarboxylic acid (II), isolated as a crystalline monohydrate. Treatment of the diester with cold alkali produced a half-ester in almost quantitative yield; the second ester group was hydrolysed only after prolonged boiling, to a product which, like the half-ester, was obtained crystalline. This difference in ease of hydrolysis of the two ester groups implies that one is subject to considerable steric hindrance, as in ethyl *meso*-2 : 5-dimethyl*cyclo*pentane-1 : 1-dicarboxylate (III) which behaves similarly (Jacobs and Florsheim, *J. Amer. Chem. Soc.*, 1950, **72**, 256). The half-ester was represented as (I; R = H, R′ = Et).

The final product of hydrolysis, while possessing the expected composition, $C_8H_8O_4$, was not the dicarboxylic acid (I; R = R′ = H). Direct titration revealed only one acid group, although, after boiling with excess of alkali, back-titration with mineral acid showed that two equivalents of alkali had been neutralised. Again, treatment with diazomethane gave a mono-, and not a di-, ester. These properties cannot be adequately explained by assuming the presence of a hindered carboxyl group in a structure such as (I; R = R′ = H);

* Part III, preceding paper.

meso-cis-2 : 6-dimethyl*cyclo*hexane-1-carboxylic acid (IV) titrates normally and is esterified on treatment with diazomethane (Jacobs, Reed, and Pacovska, *ibid.*, 1951, **73**, 4505). The final product of hydrolysis of (I; R = R′ = Et) is therefore regarded as the lactonic acid (V; R = H). A γ- rather than a δ-lactone formulation is favoured for steric reasons, and because of the infra-red evidence given below. The alternative lactonic acid structure (VI), which would result from fission of the *cyclo*propane ring by a reaction of the kind



(I) (II) (III) (IV) (V) (VI) (VII)

reported for *cyclo*propanecarboxylic acid (Perkin, *J.*, 1885, **47**, 801; cf. Fittig and Roeder, *Ber.*, 1883, **16**, 2592), its 2-ethoxy-derivative (Rambaud, *Compt. rend.*, 1949, **229**, 299), and (±)-*cis*- and (±)-*trans*-chrysanthemic acid (Crombie, Harper, and Thompson, *J. Sci. Food Agric.*, 1951, **421**), cannot be definitely excluded on the chemical evidence available, but is less consistent with the infra-red spectrum which suggests a *cyclo*propane ring.

The half-ester (I; R = H, R′ = Et), the lactonic acid (V; R = H), and the lactonic ester (V; R = Me) were each shown to contain a five-membered ring by catalytic hydrogenation over platinum. All three absorbed two mols. of hydrogen rapidly to give *cyclo*pentylmalonic acid, either directly or after hydrolysis of the saturated ester. Easy hydrogenolysis of a *cyclo*propane ring when conjugated with a double bond has been noted previously (cf. Parts I and III, *locc. cit.*), but the ease of reduction of the lactonic acid and its ester is remarkable, if these are correctly formulated as (V; R = H) and (V; R = Me). Previously only $\beta\gamma$- and $\gamma\delta$-unsaturated γ-lactones have been found to yield deoxy-acids by a reductive elimination of this type (Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601; Cocker and Hornsby, *J.*, 1947, 1157; Eisner, Elvidge, and Linstead, *J.*, 1950, 2223). The behaviour of the lactonic acid and its ester on hydrogenation thus lends some support to the allylic-type structure (VI) for the former (cf. Carter and Humiston, *J. Biol. Chem.*, 1951, **191**, 727).

At this stage in our investigations, it was clear that the diester from the malonate condensation with dibromo*cyclo*pentene was a *bicyclo*hexene, but none of the chemical or spectral evidence served to distinguish unambiguously between the favoured [3 : 1 : 0]-structure (I; R = R′ = Et), and the also conceivable [2 : 1 : 1]-structure (VII). A decision between these alternatives was, however, made possible by the following observations. Reaction of the diester with ethyl sodiomalonate, under conditions similar to those employed previously with ethyl *cyclo*propane-1 : 1-dicarboxylate and its 2-vinyl derivative (Part II; *J.*, 1952, 3616), gave a mixture of monounsaturated tetraesters. Reduction, followed by hydrolysis and decarboxylation, furnished *trans-cyclo*pentane-1 : 2-diacetic acid, identified by direct comparison with an authentic specimen. Only the *bicyclo*[3 : 1 : 0]hexene structure (I; R = R′ = Et) for the initial diester is compatible with the formation of a 1 : 2-disubstituted *cyclo*pentane. In other Michael reactions with *cyclo*propane esters the initial adduct has been largely cyclised, under the conditions employed, to a 2-keto*cyclo*pentane-1 : 3-dicarboxylate (Part II). Failure of the present tetraester to cyclise to any appreciable extent is attributable to its *trans*-configuration, which is that to be expected from addition of ethyl malonate to (I; R = R′ = Et) by a mechanism involving bimolecular nucleophilic attack of the *cyclo*propane ring.

Further support for the structures assigned to some of the compounds described above was provided by light-absorption measurements. In the infra-red region, the spectrum of the diester (I; R = R′ = Et) exhibits a strong band (5·78 μ) characteristic of an ester group, while that of the half-ester (I; R = H, R′ = Et) has strong bands (5·75 and 5·90 μ) which may be attributed to the ester and the carboxyl group. The spectrum of the lactonic acid (V; R = H) shows no ester band, but has two strong peaks (5·88 and 5·60 μ) which

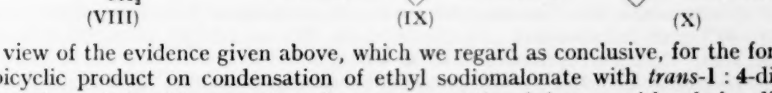
are probably due to the carboxyl group and the lactone group. Moreover, the position of the lactone band is more in agreement with that of authentic γ- (5·65 μ) than δ-lactones (5·75 μ). All three spectra have a strong maximum in the region (9·8 μ) believed to be characteristic of *cyclo*propanes (cf. Part I).

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$		$\lambda_{max.}$, Å	$\varepsilon_{max.}$
Diester (VIII) [1]	<2100	>5,000	Butadiene [2]	2170 *	20,900
Diester (I; R = R′ = Et)	2250	1,120	*cyclo*Pentadiene [3]	2440 *	2,500
Half-ester (I; R = H, R′ = Et)	2260	1,960			
Lactonic acid (V; R = H) ...	<2200	—	* In hexane.		
Lactonic ester (V; R = Me) ...	<2200	—			

[1] Kierstead, Linstead, and Weedon, *J.*, 1952, 3610. [2] Scheibe and Pummerer, *Ber.*, 1927, **60**, 2164. [3] Pickett, Paddock, and Sackter, *J. Amer. Chem. Soc.*, 1941, **63**, 1073.

Ultra-violet light absorption data are summarised in the Table. Both the diester (I; R = R′ = Et) and the half-ester (I; R = H, R′ = Et) possess a maximum at 2250—2260 Å. which is absent with the vinyl*cyclo*propanedicarboxylate (VIII). However, conjugation between the vinyl group and the *cyclo*propane ring in (VIII), which has maximal absorption below 2100 Å, is clearly shown by molecular-refractivity measurements (Part I). It is suggested that the maximum observed with both (I; R = R′ = Et) and (I; R = H, R′ = Et) is also due to electronic interaction between the double bond and the three-membered ring. The bathochromic and hypsochromic shifts of $\lambda_{max.}$ which have resulted from incorporating the vinyl*cyclo*propane chromophore in a *cyclo*pentane system are in keeping with the well-known difference in ultra-violet light absorption properties between *cyclo*pentadiene and acyclic dienes. In agreement with this interpretation, neither the lactonic acid (V; R = H) nor its ester (V; R = Me) shows maximal absorption in the 2250-Å region.

By distillation of the high-boiling residues from the preparation of (I; R = R′ = Et) two fractions were isolated These were a mixture of diesters, formed by substitution of one bromine atom in dibromo*cyclo*pentene by a malonate residue and solvolysis of the other, and a mixture of tetraesters. From the latter, by hydrogenation, hydrolysis, and decarboxylation, a crystalline *cyclo*pentanediacetic acid was obtained which differed from both the *cis*- and the *trans*-1 : 2-isomer (Linstead and Meade, *J.*, 1934, 935; Barrett and Linstead, *J.*, 1935, 436) and gave no ketone when heated with baryta. It is presumably the *trans*-1 : 3-diacetic acid derived from the tetraester (IX) in the initial mixture.



In view of the evidence given above, which we regard as conclusive, for the formation of a bicyclic product on condensation of ethyl sodiomalonate with *trans*-1 : 4-dibromo-*cyclo*pent-2-ene, it is of interest that the reaction of the *cis*-isomer with ethyl sodioacetoacetate was claimed by Reid and Yost (*J. Amer. Chem. Soc.*, 1950, **72**, 1807) to yield (70%) the *cyclo*pentadiene derivative (X). In support of this structure it was stated that the product had a permanent pale yellow colour, was strongly enolic (ferric chloride colour reaction), and on catalytic reduction absorbed 1·9 mol. of hydrogen, giving (90%) ethyl *cyclo*pentylacetoacetate. The latter argument cannot now be regarded as decisive, and the reaction will therefore be re-investigated. We find that in the malonate condensation the *cis*-dibromide gives the same diester (I; R = R′ = Et) as the *trans*-isomer, but only in about half the yield. This result may of course be due, in part, to contamination of the so-called *cis*-dibromide, which is a liquid, with the *trans*-isomer (cf. Owen and Smith, *J.*, 1952, 4035).

Experimental

Alcohol was dried as outlined in Part I (*loc. cit.*). Light-absorptions were determined in alcohol.

Condensation of 1 : 4-*Dibromo*cyclo*pent-2-ene with Ethyl Sodiomalonate*.—A solution of *trans*-1 : 4-dibromo*cyclo*pent-2-ene (60 g.; m. p. 45—46°) in alcohol (200 c.c.) was added during ½ hr. to a well-stirred, warm (70°) solution of ethyl sodiomalonate (from 85 g. of ethyl malonate and 12·2 g. of sodium) in alcohol (200 c.c.). The mixture was heated (*ca.* 90°) for 45 min. and

then cooled and poured into water. The product was isolated with ether and distilled. The portion with b. p. $<110°/0·15$ mm. was fractionated through a Stedman column (2 × 15 cm.) fitted with a total reflux, partial take-off head and gave : (i) *Ethyl* bicyclo[3 : 1 : 0]*hex-2-ene-6 : 6-dicarboxylate* (I; R = R′ = Et) (19·1 g.), b. p. 85—88°/0·15 mm., n_D^{22} 1·4678 (Found : C, 63·85; H, 7·25. $C_{12}H_{16}O_4$ requires C, 64·25; H, 7·2%). (ii) A mixture of dicarbethoxymethylethoxy*cyclo*pentenes (10·1 g., 14%), b. p. 94°/0·1 mm., n_D^{22} 1·4518 (Found : C, 62·5; H, 8·35. Calc. for $C_{14}H_{22}O_5$: C, 62·2; H, 8·2%). Hydrolysis of the mixture of esters (2·14 g.) under reflux with potassium hydroxide (1·75 g.) in water (5 c.c.) and alcohol (2 c.c.) gave an acidic product which solidified partially. Crystallisation of the solid from benzene gave a *dicarboxylic acid* (728 mg., 43%) as plates, m. p. 110° (decomp.) (Found : C, 55·8; H, 6·7%; equiv., 107. $C_{10}H_{14}O_5$ requires C, 56·05; H, 6·6%; equiv., 107).

An ethereal solution of the high-boiling residue (19 g.), from the preliminary distillation, was washed thoroughly with aqueous potassium hydroxide (2% w/v). Acidification of the alkaline extract with dilute (1 : 1) hydrochloric acid, and extraction of the oil thus liberated with ether yielded an enolic fraction (5·5 g.) which gave a wine-red colour with ferric chloride but was not examined further. The enol-free ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. Distillation gave a mixture of tetraesters (10·0 g., 10%), b. p. 120° (bath-temp.)/10^{-5} mm., n_D^{23} 1·4617 (Found : C, 59·4; H, 7·4. Calc. for $C_{19}H_{28}O_8$: C, 59·35; H, 7·35%). This was converted into *trans-cyclo*propane-1 : 3-diacetic acid as described below.

Condensation of *cis*-1 : 4-dibromo*cyclo*pent-2-ene (55·4 g.), n_D^{24} 1·5796, prepared by Blomquist and Mayes' method (*J. Org. Chem.*, 1945, **10**, 136; cf. Owen and Smith, *loc. cit.*), with ethyl sodiomalonate, in the manner described above for the *trans*-isomer, also gave ethyl *bicyclo*-[3 : 1 : 0]hex-2-ene-6 : 6-dicarboxylate (9·1 g., 17%), b. p. 90—93°/0·5 mm., n_D^{29} 1·4660.

In one experiment in which the ethyl sodiomalonate solution was added slowly to a boiling alcoholic solution of *trans*-1 : 4-dibromo*cyclo*pent-2-ene, none of the *bicyclo*hexene derivative was obtained. The main product, a *substance* separated with difficulty from recovered ethyl malonate by fractional distillation, was formed by ethanolysis of the dibromide and had b. p. 73—74°/14 mm., 177°/754 mm., n_D^{25} 1·4430 (Found : C, 69·0; H, 10·2. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

4-*Carboxymethyl*cyclo*propane*-1 : 1 : 2-*tricarboxylic Acid* (II).—A slow stream of ozonised oxygen (*ca.* 3% of O_3) was bubbled through a solution of ethyl *bicyclo*[3 : 1 : 0]hex-2-ene-6 : 6-dicarboxylate (2·0 g.) in acetic acid (" AnalaR," 15 c.c.) for 6 hr. Hydrogen peroxide (30 c.c.; 20-vol.) was then added, and the mixture was kept at 20° overnight and evaporated under reduced pressure to 5 c.c. A solution of potassium hydroxide (6·0 g.) in water (6·0 c.c.) was added, and the mixture was heated on a steam-bath for 2 hr., then cooled, extracted with ether, acidified, saturated with ammonium sulphate, and again extracted with ether (constant extractor for 2 days). Evaporation of the final ethereal extract gave a viscous oil which solidified on trituration with benzene and ether. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *tetra-acid* as a monohydrate (210 mg., 10%), m. p. 93° (Found : C, 38·05; H, 4·35. $C_8H_{10}O_9$ requires C, 38·4; H, 4·05%).

Ethyl Hydrogen bicyclo[3 : 1 : 0]*Hex-2-ene-6 : 6-dicarboxylate* (I; R = H, R′ = Et).—Ethyl *bicyclo*[3 : 1 : 0]hex-2-ene-6 : 6-dicarboxylate (2·36 g.) was shaken with a solution of potassium hydroxide (2·36 g.) in water (2·5 c.c.). The resulting brown solution was extracted with ether and then acidified with cold concentrated hydrochloric acid and saturated with ammonium sulphate. Thorough extraction with ether and evaporation of the extract gave the *half-ester* (1·92 g.), which crystallised from benzene–light petroleum (b. p. 40—60°) in rhombohedra, m. p. 68° (Found : C, 61·45; H, 6·35%; equiv., 195. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·15%; equiv., 196).

Samples of the diester prepared from both *cis*- and *trans*-1 : 4-dibromo*cyclo*pent-2-ene were hydrolysed in the above manner and gave the same half-ester, m. p. and mixed m. p. 68°.

γ-Lactone of 2-*Hydroxy*bicyclo[3 : 1 : 0]*hexane*-6 : 6-*dicarboxylic Acid* (V; R = H).—A solution of the preceding half-ester (490 mg.) and potassium hydroxide (1·0 g.) in water (5 c.c.) and alcohol (2—3 c.c.) was heated under reflux for 30 hr. Isolation of the product as in the preceding experiment gave the *lactonic acid*, which crystallised from benzene (charcoal) in plates (300 mg., 72%), m. p. 100° (Found : C, 57·45; H, 4·85%; equiv., 167 by direct titration, 84 by heating on steam-bath for ½ hr. with excess of alkali and back-titration. $C_8H_8O_4$ requires C, 57·15; H, 4·8%; equiv., 168 for $1CO_2H$, 84 for $2CO_2H$).

Treatment of the lactonic acid (1·08 g.) with diazomethane gave the *methyl* ester (0·93 g.), b. p. 103°/0·15 mm., n_D^{21} 1·4670 (Found : C, 59·4; H, 5·75. $C_9H_{10}O_4$ requires C, 59·35; H, 5·55%).

cyclo*Pentylmalonic Acid*.—(i) A solution of the half ester (I; R = H, R′ = Et) (442 mg.) in ethyl acetate (10 c.c.) was shaken in hydrogen in the presence of Adams' catalyst until absorption was complete (103 c.c. at 18°/749 mm., equiv. to 1·9 double bonds). Removal of catalyst and solvent gave an oil which was heated under reflux with a solution of potassium hydroxide (520 mg.) in water (2 c.c.) for 2 hr. Isolation of the acidic product in the usual way gave a solid (350 mg.), m. p. 145—155°, which was crystallised from benzene–ether–light petroleum (b. p. 40—60°), giving *cyclo*pentylmalonic acid (204 mg., 53%), m. p. 163° (decomp.), undepressed on admixture with an authentic specimen [Neunhoeffer, *J. pr. Chem.*, 1932, **133**, 95, gives m. p. 163° (decomp.)].

(ii) The lactonic acid (V; R = H) (300 mg.) in ethyl acetate (10 c.c.) was hydrogenated in the above manner (hydrogen absorbed, 94 c.c. at 19°/774 mm., equiv. to 2·2 double bonds). Removal of catalyst and solvent gave *cyclo*pentylmalonic acid, which crystallised from chloroform in prisms (153 mg., 50%), m. p. and mixed m. p., 162° (decomp.).

(iii) The lactonic ester (V; R = Me) (179 mg.) was hydrogenated in ethyl acetate (5 c.c.) (hydrogen absorbed, 46 c.c. at 22°/758 mm., equiv. to 1·95 double bonds). Removal of catalyst and solvent, hydrolysis of the residue, and isolation of the product as in (i), gave *cyclo*pentylmalonic acid, which crystallised from chloroform in prisms (100 mg., 60%), m. p. and mixed m. p. 162° (decomp.).

Addition of Ethyl Sodiomalonate to Ethyl bicyclo[3 : 1 : 0]*Hex-2-ene-6* : 6*-dicarboxylate* (cf. Part II).—A solution of the diester (I; R = R′ = Et) (7·0 g.) and ethyl sodiomalonate (from 5·0 g. of ethyl malonate and 0·72 g. of sodium) in alcohol (50 c.c.) was heated under reflux for 11 hr. and then cooled and poured into dilute sulphuric acid. The product was extracted with ether, and the extract washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue (7 g.) gave recovered *bicyclo*hexenedicarboxylate (4·3 g.) and a mixture of tetraesters (1·6 g.), b. p. 120° (bath-temp)/10^{-5} mm., n_D^{25} 1·4558—1·4601 (Found: C, 59·6; H, 7·45. Calc. for $C_{19}H_{28}O_8$: C, 59·35; H, 7·35%). From the alkaline extract a negligible quantity of an enolic product was obtained on acidification.

trans-cyclo*Pentane*-1 : 2*-diacetic Acid*.—A solution of the preceding mixture of tetraesters (251 mg.) in ethyl acetate (5 c.c.) was shaken in hydrogen in the presence of Adams' catalyst until absorption was complete (17 c.c. at 23°/765 mm., equiv. to 1·05 double bonds). The catalyst and solvent were removed. Concentrated hydrochloric acid (1 c.c.) was added to the residue, and the mixture heated under reflux for 17 hr. On cooling, a solid separated. Recrystallisation from water gave *trans-cyclo*pentane-1 : 2-diacetic acid (50 mg.), as cubes, m. p. 129·5—131·5° (Found: C, 58·3; H, 7·85. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%). The m. p. was undepressed on admixture with an authentic specimen, m. p. 130·5—132° (Linstead and Meade, *J.*, 1934, 935; Barrett and Linstead, *J.*, 1935, 436).

trans-cyclo*Pentane*-1 : 3*-diacetic Acid*.—A solution of the mixture of tetraesters (9·9 g.) from the condensation of *trans*-1 : 4-dibromo*cyclo*pent-2-ene with ethyl sodiomalonate, and sodium ethoxide (from 0·59 g. of sodium) in alcohol (50 c.c.) was heated under reflux for 18 hr. and then cooled and poured into dilute sulphuric acid. The product was extracted with ether, and the extract washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue gave an oil (4·9 g.), b. p. 120° (bath-temp.)/10^{-5} mm., n_D^{22} 1·4588, which was hydrogenated (Adams' catalyst) in ethyl acetate (15 c.c.), giving a mixture of saturated tetraesters (2·6 g.), b. p. 140° (bath-temp.)/10^{-4} mm., n_D^{33} 1·4520 (Found: C, 59·4; H, 8·0. Calc. for $C_{19}H_{30}O_8$: C, 59·05; H, 7·8%). This was hydrolysed under reflux with concentrated hydrochloric acid (7·5 c.c.) and gave a solid (531 mg.), m. p. 133—138°. Recrystallisation from water (charcoal) yielded trans-cyclo*pentane*-1 : 3*-diacetic acid* (355 mg.), m. p. 135·5—137·5° (Found: C, 58·3; H, 7·75%; equiv., 93. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·6%; equiv., 94). The dicarboxylic acid (180 mg.) was recovered unchanged after 1 hr.'s heating with baryta (5 mg.) at 280—290°.

The authors are indebted to Dr. L. Crombie for determining the infra-red light absorption data. Analyses and ultra-violet light absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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372. *Organic Peroxides. Part II.* Esters of the Monopercarbonic Acids.*

By A. G. Davies and K. J. Hunter.

tert.-Butyl chloroperformate (I), di-*tert.*-butyl dipercarbonate (II), *O*·*O*-*tert.*-butyl *O*-ethyl monopercarbonate (IV), and the *tert.*-butyl esters of percarbamic acid and a number of *N*-alkylpercarbamic acids (III) have been prepared as illustrated in the reaction scheme below.

Many percarboxylic esters have been prepared by the reaction of alkyl hydroperoxides with acid halides (*e.g.*, Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 642) or acid anhydrides (Davies, Foster, and White *) under basic conditions. The preparation of some alkyl monopercarbonates is now reported.

Investigation has been directed to carbonic acid derivatives because (*a*) they are structurally very similar to the known percarboxylic esters, (*b*) H_2CO_3 is a weak acid, and this should enhance the stability of the O–O bond of the resultant peresters towards heterolysis (Criegee and Dietrich, *Annalen*, 1948, **560**, 127), and (*c*) a number of salts of the monopercarbonic acids have been reported (reviewed by Partington and Fathallah, *J.*, 1950, 1934). *tert.*-Butyl hydroperoxide was chosen as the esterifying hydroperoxide because it is stable and readily prepared, and forms stable percarboxylic esters. A number of dialkyl dipercarbonates (RO·CO·O·O·CO·OR), which, however, are not peroxy-esters in the sense discussed here, have been prepared by earlier workers (Wieland, van Hove, and Borner, *Annalen*, 1925, **446**, 46; Strain, Bissinger, Dial, Rudoff, De Witt, Stevens, and Langston, *J. Amer. Chem. Soc.*, 1950, **72**, 1254; Cohen and Sparrow, *ibid.*, p. 611) by the action of sodium peroxide on alkyl chloroformates. *O*·*O*-*tert.*-Butyl *O*-*iso*propyl monopercarbonate ($Pr^iO·CO·O·OBu^t$) and impure di-*tert.*-butyl dipercarbonate [$O:C(·O·OBu^t)_2$] have also been isolated (Strain *et al.*, *loc. cit.*) by reaction of *tert.*-butyl hydroperoxide with *iso*propyl chloroformate and with carbonyl chloride respectively.

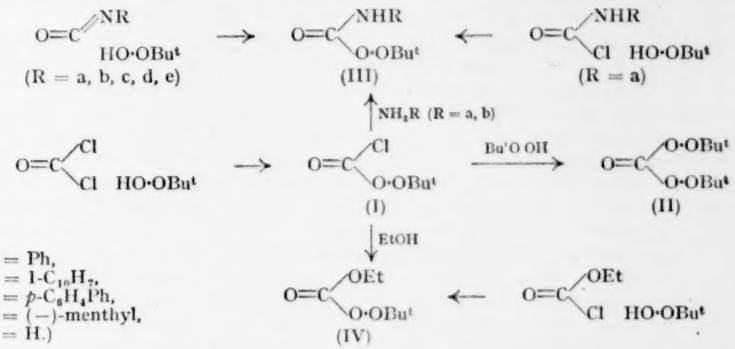
The reactions outlined in the annexed scheme have now been accomplished. We were unable to isolate pure *tert.*-butyl chloroperformate (I) from the reaction between carbonyl chloride and *tert.*-butyl hydroperoxide in the absence or presence of pyridine because decomposition apparently occurred on distillation, but it was concluded that a fraction of b. p. 30—40°/120 mm. contained a large proportion of (I) because it could be converted into the corresponding *N*-phenyl- and *N*-1-naphthyl-amides (III) in good yield. By reaction of carbonyl chloride with two mols. of the hydroperoxide in the presence of excess of pyridine, di-*tert.*-butyl dipercarbonate (II) was obtained as a stable oil.

O·*O*-*tert.*-Butyl *O*-ethyl monopercarbonate (IV) was isolated as a stable liquid after reaction of ethyl chloroformate and *tert.*-butyl hydroperoxide, and of *tert.*-butyl chloroperformate (I) and ethyl alcohol, both reactions being carried out in the presence of excess of pyridine.

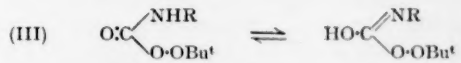
Esters (III) of the unknown percarbamic acids have been prepared by the three following types of reaction. (1) The reaction between phenyl, 1-naphthyl, and *p*-diphenylyl *iso*cyanate and *tert.*-butyl hydroperoxide proceeds readily at room temperature on the addition of a trace of pyridine, and the *tert.*-butyl *N*-arylpercarbamates (III) have been obtained as crystalline solids melting with decomposition and becoming discoloured when kept for some weeks at room temperature. *tert.*-Butyl *N*-(−)-menthylpercarbamate (III; R = menthyl), prepared by a similar reaction, is more stable, melting without decomposition and not decomposing on storage. *tert.*-Butyl percarbamate itself (III; R = H) was obtained by depolymerising cyanuric acid vapour in a red-hot tube and passing the resulting cyanic acid into a mixture of *tert.*-butyl hydroperoxide and pyridine. (2) *tert.*-Butyl *N*-phenyl- and *N*-1-naphthyl-percarbamate were also obtained by the reaction of aniline and 1-naphthylamine respectively on *tert.*-butyl chloroperformate (I). (3) *tert.*-Butyl *N*-phenylpercarbamate was prepared by treatment of *N*-phenylcarbamyl chloride with *tert.*-butyl hydroperoxide in the presence of excess of pyridine.

* Part I, *J.*, 1953, 1541.

It has been shown that *tert.*-butyl *N*-phenylpercarbamate catalyses the polymerisation of styrene at 85°, confirming that it contains a peroxide linkage which can undergo homolysis under the conditions of this experiment. Although the structures of the



derivatives of percarbamic acid are written above in the lactam form (III) the possibility of these molecules existing in prototropic equilibrium with the lactim form (III*a*) is not excluded :



The proportion of the lactim form would be expected to be largest in the case of the *N*-arylamides where stabilisation of this form will result from conjugation between the C=N double bond and the aromatic ring. The infra-red absorption spectra of *tert.*-butyl *N*-phenyl- and *N*-1-naphthyl-percarbamate demonstrate the presence of the lactam form, but the evidence for the existence of a proportion of the lactim form is inconclusive.

Experimental

tert.-Butyl hydroperoxide (b. p. 43—45°/28 mm.) was prepared by Criegee and Dietrich's method (*Annalen*, 1948, **560**, 135) on half the scale there described, precautions being taken against explosion.

tert.-*Butyl Chloroperformate* (I).—Carbonyl chloride (1·7 g.) was passed into *tert.*-butyl hydroperoxide (1·35 g.) at −10°, and the mixture then allowed to warm to room temperature during 90 min. Distillation, apparently accompanied by decomposition, yielded impure *tert.*-butyl chloroperformate (0·8 g.), b. p. 30—40°/120 mm. This was the material used in the preparation of *tert.*-butyl *N*-phenyl- and *N*-1-naphthyl-percarbamate. No advantage was gained by addition of pyridine to the reaction mixture, or by short-path distillation of the product at room temperature.

Di-tert.-*butyl Dipercarbonate* (II).—A toluene solution of carbonyl chloride (85 g. of 12½% solution) was added at 0° during 30 min. to a stirred solution of *tert.*-butyl hydroperoxide (16·2 g.) in pyridine (35 g.). After 60 min., water was added and the toluene layer separated and thoroughly washed with 5% hydrochloric acid and water. From the toluene solution *di*-tert.-*butyl dipercarbonate* (15 g.) was recovered, having b. p. 54—55°/0·5 mm., n_D^{25} 1·4139, d_4^{25} 0·975 (Found : C, 53·0; H, 8·6. $C_9H_{18}O_5$ requires C, 52·4; H, 8·8%).

O•O-tert.-*Butyl* O-*Ethyl Monopercarbonate* (IV).—(a) *From ethyl chloroformate.* To a mixture of ethyl chloroformate (5·0 g.) and *tert.*-butyl hydroperoxide (4·1 g.) at 0°, pyridine (7 g.) was added dropwise, a vigorous reaction taking place and pyridine hydrochloride being precipitated. Ether was added and the solution washed with water and sodium hydrogen carbonate solution, and dried (Na_2SO_4). Distillation of the ethereal solution yielded three fractions of 1·8 g. each, *viz.*, b. p. (i) 28—30°, (ii) 30°, (iii) 30—32°, all at 0·8 mm. The middle fraction was redistilled giving OO-tert.-*butyl* O-*ethyl monopercarbonate*, b. p. 30°/0·8 mm., n_D^{20} 1·4052, d_4^{20} 0·984 (Found : C, 51·8; H, 8·5. $C_7H_{14}O_4$ requires C, 51·8; H, 8·7%).

(b) *From* tert.-*butyl chloroperformate.* Carbonyl chloride (2 g.) and *tert.*-butyl hydroperoxide (1·4 g.) were allowed to react together at 0° for 1 hr. and then nitrogen was passed through the solution at room temperature to sweep out hydrogen chloride gas and any unchanged carbonyl

chloride. Absolute ethyl alcohol (0·7 g.) was then added, followed by excess of pyridine (2 g.) dropwise at 3—5°. After 30 min., iced water was added and the solution extracted twice with ether. The combined ethereal extracts were washed with dilute aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and distilled, yielding *OO-tert.*-butyl *O*-ethyl monopercarbonate (1·0 g.), b. p. 64°/15 mm., n_D^{20} 1·4057 (Found : C, 51·9; H, 9·0%).

tert.-*Butyl* N-*Phenylpercarbamate* (III; R = Ph).—(a) *From phenyl* iso*cyanate*. To a mixture of *tert.*-butyl hydroperoxide (2·7 g.) and phenyl *iso*cyanate (3·6 g.), pyridine (0·05 g.) was added, the temperature of the mixture being kept below 40°. After about 15 min. the mixture solidified to an orange-white solid which was extracted with cold benzene (60 c.c.), leaving a residue of *s*-diphenylurea (0·2 g.; m. p. 242°). The benzene was evaporated off at room temperature, leaving a solid (2·3 g.) which was recrystallised twice from ether–light petroleum. tert.-*Butyl* N-*phenylpercarbamate* (1·7 g.) was obtained as colourless crystals, m. p. 83° (decomp.) (Found : C, 63·6; H, 7·25; N, 6·45. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%). Although this was stable at 0° for some months, after 2—3 weeks at room temperature a brown colour developed and a smell resembling that of phenyl *iso*cyanide became apparent. When the reaction was carried out in benzene solution no *s*-diphenylurea was obtained, and a better yield of colourless (III; R = Ph) separated from the mixture.

(b) *From* tert.-*butyl chloroperformate*. After 12 hr., the precipitate obtained by adding excess (0·5 g.) of aniline to *tert.*-butyl chloroperformate (0·3 g.) was filtered off, washed with dilute hydrochloric acid and water, and dried. Recrystallisation from ether–light petroleum yielded (III; R = Ph) (0·2 g.), m. p. 82° (decomp.), undepressed on admixture with the product obtained from phenyl *iso*cyanate.

(c) *From N-phenylcarbamyl chloride*. Phenylcarbamyl chloride was prepared by passing hydrogen chloride gas into phenyl *iso*cyanate (3·3 g.) initially at 20° and later at 55°, till the mass solidified (Lengfeld and Stieglitz, *Amer. Chem. J.*, 1894, **16**, 71; Hentschel, *Ber.*, 1885, **18**, 1178). The product was dried in a vacuum-desiccator; it (3·25 g.) then showed m. p. 57—58°. Phenylcarbamyl chloride (0·5 g.) was dissolved in *tert.*-butyl hydroperoxide (0·9 g.), and pyridine (1·9 g.) added; after 15 min. at 0° the mixture was poured on iced water, and the precipitated solid (0·47 g.) recrystallised from ether–light petroleum, yielding *tert.*-butyl *N*-phenylpercarbamate, m. p. 83° (decomp.), undepressed on admixture with the product obtained from phenyl *iso*cyanate.

tert.-*Butyl* N-1-*Naphthylpercarbamate* (III; R = 1-naphthyl).—(a) *From* 1-*naphthyl* iso*cyanate*. After 12 hr., from a mixture of *tert.*-butyl hydroperoxide (0·9 g.), 1-naphthyl *iso*cyanate (1·7 g.), and pyridine (0·05 g.) in benzene (3 c.c.) the solid (1·4 g.) which had been precipitated was filtered off and recrystallised from ether–light petroleum. tert.-*Butyl* N-1-*naphthylpercarbamate* was obtained as pale buff crystals, m. p. 80° (decomp.) (Found : C, 69·7; H, 6·7; N, 5·3. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·6; N, 5·4%).

(b) *From* tert.-*butyl chloroperformate*. 1-Naphthylamine (0·60 g.) was added to *tert.*-butyl chloroperformate (0·30 g.) in ether at <20°. After 20 min. the precipitated 1-naphthylamine hydrochloride was filtered off and washed with ether. The combined ethereal layers were washed with dilute hydrochloric acid and water, and dried (Na_2SO_4), and the solvent evaporated off, yielding *tert.*-butyl *N*-1-naphthylpercarbamate, which, recrystallised from ether–light petroleum, showed m. p. 79° (decomp.) alone and when mixed with the specimen obtained from 1-naphthyl *iso*cyanate.

tert.-*Butyl* N-p-*Diphenylylpercarbamate* (III; R = *p*-diphenylyl).—To a mixture of *tert.*-butyl hydroperoxide (0·72 g.) and *p*-diphenylyl *iso*cyanate (1·55 g.) in benzene (20 c.c.) at 0°, pyridine (0·05 g.) was added; after 20 min. an orange colour slowly developed. Next morning the solution was filtered from a small amount of *s*-di-*p*-diphenylylurea and evaporated to dryness. The crude tert.-*butyl* N-p-*diphenylylpercarbamate* (0·85 g.) obtained was recrystallised from ether–light petroleum, forming pale buff needles, m. p. 85° (decomp.) (Found : C, 71·6; H, 6·8; N, 5·1. $C_{17}H_{19}O_3N$ requires C, 71·5; H, 6·7; N, 4·9%).

tert.-*Butyl* N-(−)-*Menthylpercarbamate* [III; R = (−)-menthyl].—A solution of *tert.*-butyl hydroperoxide (0·23 g.), (−)-menthyl *iso*cyanate (0·47 g.; $[\alpha]_D^{22}$ −64·2°), and pyridine (0·06 g.) in dry benzene (5 c.c.) was kept at room temperature for 12 hr. The solvent was evaporated off under vacuum and the colourless solid obtained (0·7 g.) was recrystallised twice from light petroleum, yielding tert.-*butyl* N-*menthylpercarbamate*, m. p. 101°, $[\alpha]_D^{18}$ −59° ± 2° (l = 1, c = 0·761 in $CHCl_3$) (Found : C, 66·3; H, 10·5; N, 5·65. $C_{15}H_{29}O_3N$ requires C, 66·4; H, 10·8; N, 5·2%).

tert.-*Butyl Percarbamate* (III; R = H).—Sublimed cyanuric acid (0·4 g.) was led in a current of dry air through a 6-inch length of red-hot Pyrex tubing, and the resulting cyanic

acid condensed into a mixture of *tert.*-butyl hydroperoxide (0·85 g.) and pyridine (0·10 g.) cooled in ice–ammonium chloride. After 12 hr. at room temperature the mixture was extracted with ether, to yield a white crystalline solid (0·15 g.), m. p. 47—48°. Recrystallisation from ether–light petroleum gave tert.-*butyl percarbamate* (0·10 g.), m. p. 51° (Found: C, 44·6; H, 8·0; N, 10·2. $C_5H_{11}O_3N$ requires C, 45·1; H, 8·3; N, 10·5%).

We are indebted to Dr. G. J. Minkoff for recording and interpreting the infra-red absorption spectra of *tert.*-butyl *N*-phenyl- and *N*-1-naphthyl-percarbamate.

CHEMISTRY DEPARTMENT, BATTERSEA POLYTECHNIC, S.W.11. [*Received, February 9th,* 1953.]

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373. *Cinnolines. Part XXXI.* The Nature of the $C_{(3)}$-Position. Some Experiments with 3-Substituted Cinnolines.*

By E. J. ALFORD and K. SCHOFIELD.

The structure of 3-hydroxycinnoline was proved by its conversion into 3-chloro- and its formation from 3-bromo-cinnoline. Methylation of 3-hydroxycinnoline under acidic conditions, or with ethereal diazomethane, gave 2 : 3-dihydro-3-keto-2-methylcinnoline which was reduced to the 1 : 2 : 3 : 4-tetrahydro-3-keto-derivative, and also to oxindole and methylamine.

4-Methylcinnoline reacted readily with chloral, and 3-methylcinnoline methiodide gave in small yield a derivative with *p*-dimethylaminobenzaldehyde.

3-Aminocinnoline was obtained from 3-chloro- and 3-bromo-cinnoline. pK_a and ultra-violet absorption spectra determinations are presented which indicate that 3-hydroxycinnoline exhibits lactam–lactim tautomerism, and that $N_{(2)}$ is the basic centre in 3-aminocinnoline.

WE have previously described the synthesis of 3-hydroxy-,† 3-methyl-, 3-chloro-, and 3-bromo-cinnoline (*J.*, 1952, 2102; 1953, 609), and now record preliminary experiments with these compounds, bearing on the interplay between $N_{(2)}$ and $C_{(3)}$ in cinnoline derivatives.

(A) 3-*Hydroxycinnoline.*—This compound gave with phosphorus oxychloride a small yield of 3-chlorocinnoline. Although the hydroxy-compound readily formed a benzoate (Alford and Schofield, *loc. cit.*), we were unable to obtain an acetate. pK_a values for 3-hydroxycinnoline (8·64) and 3-hydroxyquinoline (8·07) were determined in water at 20°.

With methyl sulphate and a deficiency of sodium hydroxide, 3-hydroxycinnoline gave the bright yellow 2 : 3-dihydro-3-keto-2-methylcinnoline (I). This was also formed from 3-hydroxycinnoline and ethereal diazomethane, a reagent which was without effect on the more feebly acidic 4-hydroxycinnoline, but converted 3-hydroxy- into 3-methoxy-quinoline. 2 : 3-Dihydro-3-keto-2-methylcinnoline was decomposed to a tar by alkali. Neber, Knöller, Herbst, and Trissler (*Annalen*, 1929, **471**, 127) reduced 3-hydroxycinnoline with red phosphorus and hydriodic acid to ammonia and oxindole, and (I) similarly gave methylamine and oxindole. Milder reduction of (I) provided a pale yellow tetrahydro-compound, presumably (II). 2 : 3-Dihydro-3-keto-2-methylcinnoline appeared to give a methiodide but this could not be purified.

The tar formed when 3-hydroxycinnoline was treated with methyl sulphate and excess of alkali yielded a small amount of an orange product. The high m. p. of this substance excluded its formulation as 3-methoxycinnoline and it is tentatively regarded as (III).

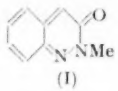
Although 3-hydroxy- gave 3-amino-quinoline in a Bucherer reaction, 3-hydroxycinnoline was unchanged by this process.

(B) 3-*Methylcinnoline.*—Unlike 4-methylcinnoline, which provided (IV), the 3-methyl isomer did not react with chloral in pyridine. It did, however, readily form a methiodide, which reacted with *p*-dimethylaminobenzaldehyde to give a small yield of the deeply coloured styryl compound (V). No product could be isolated from reactions between the

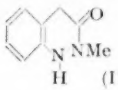
* Part XXX, *J.*, 1953, 609. † The term "3-hydroxycinnoline" is used throughout without implications for the fine structure of the compound.

methiodide and *p*-dimethylaminobenzaldehyde under the conditions used by Brooker and White (*J. Amer. Chem. Soc.*, 1951, **73**, 1094).

(C) *3-Halogenocinnolines.*—3-Bromocinnoline reacted with methanolic sodium methoxide at 110—120° to give 3-methoxycinnoline, isolated as its picrate. In a similar experiment in undried methanol, the sodium salt of 3-hydroxycinnoline was obtained in good yield. Several attempts to convert 3-bromo- and 3-chloro- into 3-hydroxy-cinnoline by Maier-Bode's method (*Ber.*, 1936, **69**, 1534) gave only traces of the desired product.



(I)



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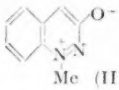
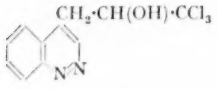
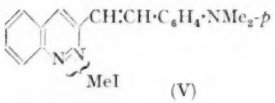


(III)



(IV)



(V)

It was shown by Schofield and Swain (*J.*, 1950, 384) that 3-bromo-4-chlorocinnolines were converted by phosphorus oxychloride into 3 : 4-dichlorocinnolines, more rapidly at 95° than at 135°. We now find 3-bromocinnoline, on the basis of carbon analyses, to behave similarly, though more slowly.

3-Bromocinnoline was reduced to cinnoline by hydrazine in alkaline medium with a palladium catalyst (Busch and Weber, *J. pr. Chem.*, 1936, **146**, 1).

3-Bromo- and 3-chloro-cinnoline reacted with ammonia under pressure in the presence of copper sulphate (Maier-Bode, *loc. cit.*) to give 3-aminocinnoline. The chloro-compound requires a higher reaction temperature than the bromo-compound.

(D) *3-Aminocinnoline.*—In contrast to 3-aminoquinoline, the cinnoline is yellow, and its yellowish-green aqueous solution exhibited greenish-blue fluorescence, to be compared with the violet fluorescence of the quinoline derivative. 3-Aminocinnoline readily formed an acetyl derivative. 3-Aminoquinoline is readily diazotised, and the diazonium solution forms a deep red azo-compound with α-naphthol (Mills and Watson, 1910, **97**, 741), but in a similar test 3-aminocinnoline gave merely a reddish-brown solution. This reaction requires rigorous examination, but it seems that 3-aminocinnoline does not readily form a diazonium salt, if it does so at all.

pK_a values for 3-aminocinnoline (3·63) and 3-aminoquinoline (4·96) were determined in water. The value for 3-aminoquinoline confirms that given by Albert, Goldacre, and Phillips (*J.*, 1948, 2240).

Experimental

Extracts were dried with anhydrous sodium sulphate.

(A) *Replacement of Hydroxy- by Chloro-group.*—3-Hydroxycinnoline (0·5 g.) and phosphorus oxychloride (10 c.c.) were refluxed together for 8 hr. The mixture was decomposed with ice and sodium hydroxide, and extracted with ether. The extract yielded 3-chlorocinnoline (0·05 g.), m. p. 90—91°, alone and mixed with an authentic specimen (Alford and Schofield, *loc. cit.*).

Methylation.—(i) 3-Hydroxycinnoline (5 g.), water (25 c.c.), and half of a solution of sodium hydroxide (1·5 g.) in water (40 c.c.) were stirred at 95° and treated during 10 min. with methyl sulphate (4·5 c.c.), and the other half of the alkali solution was then added dropwise. After being stirred at the same temperature for 20 min. more, the product was extracted with chloroform. Concentration provided a solid (5·05 g.; m. p. 125—130°) which separated from acetone as golden-yellow plates (3·0 g.) of 2 : 3-*dihydro*-3-*keto*-2-*methylcinnoline*, m. p. 135·5—136·5° (Found : C, 67·1; H, 5·4. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%). The aqueous solution of the compound exhibited a powerful green fluorescence. With hot alkali the substance formed a tar, and a deep green colour developed.

(ii) An experiment on the same scale with 2N-alkali (40 c.c.) and methyl sulphate (6 c.c.) gave a dark solution and much tar. Treatment of the tar with hot acetone left undissolved a yellow solid (0·17 g.), which was recrystallised from alcohol and from chloroform–ligroin; it formed

orange plates of the *anhydro*-salt (III), m. p. 280—283°, of 3-hydroxy-1-methylcinnolinium hydroxide (Found: C, 68·8; H, 4·9. $C_9H_8ON_2$ requires C, 67·5; H, 5·9%).

(iii) 3-Hydroxycinnoline (0·5 g.) dissolved with effervescence during ½ hr. in an ethereal solution of diazomethane (from 1 c.c. of methylnitrosourethane). Filtration and evaporation gave glistening yellow plates (0·27 g.) of 2 : 3-dihydro-3-keto-2-methylcinnoline, m. p. 132—134°, after crystallisation from benzene. More of this product was obtained from the ethereal mother-liquor.

(iv) 3-Hydroxyquinoline (0·5 g.) similarly dissolved during ¼ hr. in ethereal diazomethane. Next morning the solution was evaporated, leaving 3-methoxyquinoline (0·57 g.) as a dark oil. *3-Methoxyquinoline picrate*, prepared from alcoholic solutions of the components, crystallised from dioxan as orange prisms, m. p. 220—222° (Found: C, 50·0; H, 3·3. $C_{10}H_9ON,C_6H_3O_7N_3$ requires C, 49·5; H, 3·1%).

Reduction of 2 : 3-*Dihydro*-3-*keto*-2-*methylcinnoline*.—(i) The keto-derivative (1 g.), alcohol (20 c.c.), and zinc dust (5 g.) were refluxed together during the addition of aqueous ammonia (15 c.c.; *d* 0·88) in portions (2·5 c.c.) during ¾ hr. After refluxing for a total of 1 hr., the initial green fluorescence had disappeared, and the colourless solution was refluxed for 5 hr. more and then evaporated to dryness *in vacuo*. The residue crystallised from benzene–ligroin as light yellow crystals (0·44 g.). Pure 1 : 2 : 3 : 4-*tetrahydro*-3-*keto*-2-*methylcinnoline*, m. p. 91—92·5° (Found: C, 66·2; H, 6·1; N, 17·7. $C_9H_{10}ON_2$ requires C, 66·6; H, 6·2; N, 17·3%), was colourless.

(ii) The dihydroketo-derivative (1 g.), red phosphorus (1 g.), and hydriodic acid (10 c.c.; *d* 1·65—1·70) were refluxed together for 8 hr. After cooling and filtration, colourless needles separated. Water was added to dissolve these, and the solution was filtered, neutralised with sodium hydroxide, and extracted with ether. The residue (0·45 g.) from the extract was recrystallised from water, and then from benzene–ligroin (b. p. 100—120°), and finally from ligroin, giving colourless needles of oxindole, m. p. 125—126·5° (Found: C, 72·6; H, 5·45. Calc. for C_8H_7ON: C, 72·2; H, 5·3%), identical with a specimen similarly obtained from 3-hydroxycinnoline (Neber *et al.*, *loc. cit.*).

To the neutral aqueous reaction solution remaining after ether-extraction was added 4N-sodium hydroxide (20 c.c.) and water (20 c.c.), and the resulting solution was distilled into hydrochloric acid (80 c.c.; 4N) until only a small amount of the original remained. The acid solution was evaporated, leaving a solid residue (0·37 g.). A portion (0·2 g.) of this, acetic acid (5 c.c.), phthalic anhydride (0·2 g.), and anhydrous sodium acetate were refluxed together for 1 hr. The hot solution was filtered and evaporated, giving colourless needles of *N*-methylphthalimide (0·13 g.), m. p. 133—135 (unchanged by crystallisation from acetic acid and vacuum-sublimation) (Found: C, 67·6; H, 4·5. Calc. for $C_9H_7O_2N$: C, 67·1; N, 4·4%), identical with an authentic specimen. The remainder of the residue was treated with picric acid in hot water and gave methylamine picrate, yellow prisms, m. p. 208—212° (decomp.), from ethyl acetate, identical with an authentic specimen.

Conversion of 3-*Hydroxy- into* 3-*Amino-quinoline*.—3-Hydroxyquinoline (0·5 g.), saturated ammonium sulphite solution (7 c.c.), and aqueous ammonia (7 c.c.; *d* 0·88) were heated for 8 hr. at 130—140°. Sodium hydroxide was added, and the mixture extracted with ether. Removal of the solvent gave crude 3-aminoquinoline (0·05 g.), m. p. after crystallisation from toluene, 80—83°.

(B) 4-(3 : 3 : 3-*Trichloro*-2-*hydroxypropyl*)*cinnoline*.—4-Methylcinnoline (2 g.), pyridine (5 c.c.), and chloral (2·2 g.) were heated at 95° for 2 hr. When poured into water, the solution gave an oil which quickly solidified, giving 3·85 g. of product. 4-(3 : 3 : 3-*Trichloro*-2-*hydroxypropyl*)*cinnoline* separated from ethanol as glistening silver leaflets, m. p. 165—166° (decomp.) (Found: C, 45·5; H, 3·0. $C_{11}H_9ON_2Cl_3$ requires C, 45·3; H, 3·1%).

3-*Methylcinnoline Methiodide*.—When 3-methylcinnoline (1·25 g.) and methyl iodide (1·25 c.c.) were dissolved together in ethanol (8 c.c.), heat was evolved and the solution became red. After being refluxed for 2½ hr. and then cooled the mixture deposited orange leaflets (1·31 g.), m. p. 202—205·5° (decomp.). Concentration gave a second crop (0·73 g.), m. p. 147—149°. Recrystallisation from methanol gave red needles of 3-*methylcinnoline methiodide*, m. p. 204—206·5° (decomp.) (Found: C, 41·75; H, 3·7. $C_{10}H_{11}N_2I$ requires C, 42·0; H, 3·9%). This was readily soluble in water, and addition of sodium hydroxide produced a transient blue colour which changed to green, and was followed by precipitation of amorphous green material which could not be crystallised.

The methiodide (0·36 g.) and *p*-dimethylaminobenzaldehyde (0·25 g.) were added to boiling acetic anhydride (25 c.c.), and the mixture was refluxed for 1¼ hr., then stored overnight; a

dark green crystalline product (0·07 g.), m. p. 330—335°, was collected. This separated as black crystals (with a green reflex), m. p. 353—355° (decomp.), from its deep blue solution in alcohol, and a further crystallisation produced a brownish powder, decomposing at about 370° and still impure (Found: C, 56·6; H, 5·2; N, 11·6. Calc. for $C_{19}H_{20}N_3I$: C, 54·7; H, 4·8; N, 10·1%). When the experiment was repeated with carefully purified reactants at 160° for 2 hr. the product (not recrystallised), m. p. 335—340° (decomp.), had a more satisfactory analysis (Found: C, 56·0; H, 4·8; N, 9·1%). The dark colour of the compound was destroyed by acids and alkalis.

(C, D) *Halogen Exchange.*—3-Bromocinnoline (0·2 g.) and phosphorus oxychloride (2 c.c.) were refluxed together for 2 hr. A clear green solution was formed with no obvious evolution of bromine. The product (0·16 g.; m. p. 91—92·5°), isolated in the usual way and crystallised once from light petroleum, had m. p. 92·5—93° (Found: C, 47·1; H, 2·3. Calc. for $C_8H_5N_2Br$: C, 45·9; H, 2·4. Calc. for $C_8H_5N_2Cl$: C, 58·35; H, 3·1%). From a similar experiment (with 3 c.c. of phosphorus oxychloride) carried out at 95°, the product (0·18 g.; m. p. 80—90°) after one crystallisation had m. p. 90—91° (Found: C, 49·2; H, 2·4%).

Reduction of 3-Bromocinnoline.—3-Bromocinnoline (0·25 g.), methanolic potassium hydroxide (3 c.c., 5%), palladised charcoal (0·15 g., 5%), and hydrazine hydrate (0·1 g., 90%) were refluxed for 2 hr. Water (3 c.c.) was then added and an oil extracted with ether. The picrate (0·24 g.; m. p. 185—190°) from this product crystallised from dioxan as orange prisms (0·15 g.), m. p. 191—194°, giving no m. p. depression with cinnoline picrate.

Conversion of Bromo- into Amino-group.—3-Bromocinnoline (0·5 g.), copper sulphate (0·06 g.), and aqueous ammonia (8 c.c.; *d* 0·88) were heated for 20 hr. at 130—140°. The mixture was warmed to remove ammonia, treated with water (5 c.c.) and 4N-sodium hydroxide (10 c.c.), and extracted with ether. The crude product (0·49 g.) was recrystallised from ethyl acetate, giving 3-*aminocinnoline* (0·37 g.), which when pure formed clusters of yellow needles, m. p. 165—166·5° (Found: C, 66·1; H, 5·2. $C_8H_7N_3$ requires C, 66·2; H, 4·9%), from ethyl acetate–ligroin (b. p. 60—80°). The same yield of amine was obtained from 3-chlorocinnoline only at 160—170°. The amine and acetic anhydride, when refluxed together for 5 min. and then poured into water, gave colourless crystals. Crystallisation from water provided silky needles of 3-*acetamidocinnoline*, m. p. 225—226° (Found: C, 64·6; H, 4·8. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·85%).

Replacement of Bromo- by Methoxy- and Hydroxy-groups.—3-Bromocinnoline (0·25 g.) and a solution of sodium (0·13 g.) in dry methanol (4 c.c.) were heated in a sealed tube for 17 hr. at 110—120°. The resultant solution was diluted with water and extracted with ether. From the extract, 3-methoxycinnoline was isolated as a pale yellow oil which slowly crystallised (0·24 g.; m. p. 40—42°) but was not purified. Its *picrate*, formed from alcoholic solution, crystallised from the same solvent as yellow prisms, m. p. 155—157·5° (Found: C, 46·9; H, 2·8. $C_9H_8ON_2,C_6H_3O_7N_3$ requires C, 46·3; H, 2·85%).

The reaction solution from an experiment on twice the above scale, but with undried methanol, on cooling deposited large yellow plates of the sodium salt, m. p. >270°, of 3-hydroxycinnoline. From the aqueous solution of this compound on acidification with dilute acetic acid, there separated yellow crystals (0·25 g.), m. p. 200—202°, of 3-hydroxycinnoline, identified by conversion into 3-benzoyloxycinnoline.

*Physical Determinations.**—pK_a values for 3-hydroxy-cinnoline and -quinoline were determined in 0·002M-aqueous solution at 20° ± 0·1°, by potentiometric titration with aqueous sodium hydroxide (0·11N), a glass electrode and a Cambridge pH meter being used. The blue fluorescence of dilute aqueous solutions of 3-hydroxyquinoline was diminished in intensity by the titration, but not extinguished. Values for 3-amino-cinnoline and -quinoline were determined similarly in M/90-aqueous solution, by titration with 0·91N-hydrochloric acid.

Ultra-violet absorption spectra were measured in the usual way by means of a Unicam Spectrophotometer, Model SP 500.

Discussion

There is much evidence that heterocyclic nitrogen compounds formally containing α- or γ-hydroxyl groups may exist predominantly as the keto-forms (Ewing and Steck, see Table; Elderfield, "Heterocyclic Compounds," Wiley and Sons, New York, 1952, Vol. 4, pp. 137, 439; Marshall and Walker, *J.*, 1951, 1004; Albert, "The Acridines," London, 1951, p. 326), though not necessarily so (Albert, *op. cit.*). The case of 3-hydroxycinnoline is interesting

* Full details will be found in the Ph.D. thesis of E. J. Alford, London, 1952.

from this point of view, an analogous example with both the nitrogen atom and the $-C(OH)-$ unit at β-positions in the bicyclic structure evidently not having been described before. We have now tried to establish that the phenolic structure (VI) is not adequate as a representation of 3-hydroxycinnoline, without attempting quantitative assessment of the importance of the lactam form.

Longuet-Higgins and Coulson's calculations (*J.*, 1949, 971) suggest that the structure (VI) would be more acidic than 3-hydroxyquinoline, itself a true phenol [the calculations are borne out in the case of 4- (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356) and 8-hydroxycinnoline (Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009), compared with the quinoline analogues], but the reverse is actually the case. This suggests that lactam–lactim tautomerism is of significance in 3-hydroxycinnoline.

Consistent with this view are the absorption spectra of 3-hydroxycinnoline and 2 : 3-dihydro-3-keto-2-methylcinnoline. [The structure of the methyl compound is proved by its reduction to methylamine and oxindole, the latter probably arising from the cyclisation of an acyclic intermediate with extrusion of $N_{(2)}$, a type of elimination conclusively established in the similar case of the Fischer indole synthesis (Clusius and Weisser, *Helv. Chim. Acta*, 1952, **35**, 400).] The spectrum of 3-hydroxycinnoline in methanol differs only slightly from that in water (see Table), but in alkaline solution a hypsochromic shift occurs owing to ionisation of the compound. By contrast, the absorption in acid medium differs little from that in water. This recalls the behaviour of carbostyril and *iso*carbostyril (Ewing and Steck, *loc. cit.*) which, probably being weaker acids than 3-hydroxycinnoline, show no change even in alkaline solution. Thus the curves suggest the possibility of lactam–

Absorption spectra.

		λ (mμ), $\log_{10}\varepsilon$				
	Solvent	Max.	Min.	Max.	Min.	Max.
3-Hydroxyquinoline	95% MeOH	—	262, 3·29	286, 3·33	300, 3·16	322, 3·59 333, 3·64
	95% EtOH *	234, 4·43	258, 3·43	270, 3·46 279, 3·46	300, 3·20	321, 3·63 336, 3·65
	0·01N-HCl *	240, 4·40	266, 2·72	315, 3·60	321, 3·56	345, 3·72
	0·01N-NaOH *	235, 4·32	—	—	303, 2·78	350, 3·73
3-Hydroxycinnoline	95% MeOH	—	—	300, 2·84 312, 2·76	321 325 2·6	400, 3·47
	H_2O	226, 4·67	292, 2·87	300, 2·93 312, 2·89	324, 2·58	394, 3·51
	0·01N-HCl	—	287, 2·82	300, 2·88	323, 2·56	398, 3·46
	0·01N-NaOH	—	—	—	314, 2·38	385, 3·62
2 : 3-Dihydro-3-keto-2-methylcinnoline	95% MeOH	—	285, 3·02	305, 3·12	329, 2·59	400, 3·51
	0·01N-HCl	—	286, 2·94	303, 3·06	326, 2·53	400, 3·50
	0·01N-NaOH	—	283, 2·90	303, 3·12	328, 2·58	395, 3·52
3-Chlorocinnoline	95% MeOH	—	255, 3·04	285, 3·33	308, 3·09	330, 3·43
	0·01N-HCl	—	260, 2·98	285, 3·28	308, 3·09	335, 3·42
	0·01N-NaOH	—	258, 3·07	285, 3·40	308, 3·22	338, 2·54
3-Aminocinnoline	95% MeOH	237, 4·59	—	—	312, 2·79	385, 3·43
	0·01N-HCl	235, 4·59	305, 2·79	310, 2·88 315, 2·83	320, 340 2·68	405, 3·45
	0·01N-NaOH	233, 4·53	—	—	312, 2·60	372, 3·36

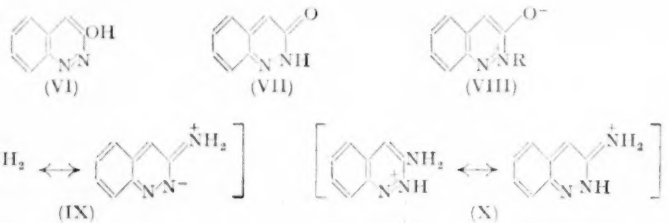
* See also Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

lactim tautomerism in 3-hydroxycinnoline, and the close similarity between the spectra of 3-hydroxycinnoline and 2 : 3-dihydro-3-keto-2-methylcinnoline reinforces this conclusion, although until 3-methoxycinnoline becomes available the evidence is not complete. The insignificant changes in the spectrum of the keto-derivative in passing from alkaline to acid medium are consistent with its structure. In contrast to those of 3-hydroxycinnoline, the curves for 8-hydroxycinnoline (Alford *et al.*, *loc. cit.*) and 3-hydroxyquinoline show appreciable differences depending on pH, as would be expected, both the phenolic and basic properties of these compounds being well developed.

From the foregoing it is apparent that lactam–lactim tautomerism is possible in 3-

hydroxycinnoline, although owing to the particular structure of the lactam the acidic nature of the lactim is more developed than in such a substance as carbostyril. The lactam would be represented in classical terms by the *o*-quinonoid structure (VII) but, it being borne in mind that 2 : 3-naphthaquinone is unknown, a better representation of this and 2 : 3-dihydro-3-keto-2-methylcinnoline is probably (VIII; R = H or Me) (Huisgen, *Annalen*, 1948, **559**, 101).

These observations, clearly indicating interaction between $N_{(2)}$ and a 3-substituent, raised our interest in 3-methylcinnoline. Formerly, reactivity in methyl groups in heterocyclic molecules was believed to depend on the existence of the elements of structure ·N:CMe· and ·N:C·C:CMe· (Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1937, p. 558). For this reason the ability of 4-methylcinnoline ethiodide to react with *p*-dimethylaminobenzaldehyde (Atkinson and Simpson, *J.*, 1947, 808) has been held to prove that in 4-methylcinnoline $N_{(1)}$ is the basic centre. 4-Methylcinnoline itself condenses with benzaldehyde in the presence of zinc chloride (Jacobs, Winstein, Henderson, and Spaeth, *J. Amer. Chem. Soc.*, 1946, **68**, 1310). Recently, however, Erlenmeyer, Brumann, and Sorkin (*Helv. Chim. Acta*, 1948, **31**, 1978) condensed 3-methyl*iso*quinoline with benzaldehyde, and Brooker and White (*loc. cit.*) condensed 3-methyl*iso*quinoline methiodide with *p*-dimethylaminobenzaldehyde, though reactivity was much less pronounced than in the 1-methyl series. Apparently a methyl group adjacent to a ring nitrogen will always be activated to some extent, considerably if the nitrogen–carbon link possesses a high degree of double-bond character. Our experiments demonstrate the lower reactivity of the 3- than of the 4-methyl group in cinnolines, but stress the need for caution in deducing the site of quaternisation from such reactivity in quaternary salts (the yields of products obtained from 3- and 4-methylcinnoline methiodides and *p*-dimethylaminobenzaldehyde were similar), and raise the interesting possibility that 3-methylcinnoline may quaternise on $N_{(2)}$. We are investigating this.



The conversion of 3-hydroxy- into 3-chloro-cinnoline, and of 3-bromo- into 3-hydroxycinnoline, completes the proof of the structure of the latter product obtained by Bossel's method (Alford and Schofield, *loc. cit.*), which previously depended on its reduction to oxindole (Neber *et al.*, *loc. cit.*). Such conversions and the similar formation of 3-aminocinnoline are not, however, sufficient to reveal activation in the 3-halogen atoms. 3-Bromoquinoline has been aminated similarly (Kuhn and Westphal, *Ber.*, 1940, **73**, 1105). The formation of cinnoline by hydrazine reduction of 3-bromocinnoline indicates some degree of activation, for the more normally " aromatic " halogen compounds behave differently, 3-bromopyridine, for example, giving 3 : 3′-dipyridyl (Busch and Weber, *loc. cit.*). The absorption spectrum of 3-chlorocinnoline generally resembles that of cinnoline (Hearn, Morton, and Simpson, *J.*, 1951, 3318), modified slightly by the auxochromic chlorine atom. It is not surprising that the spectrum of such a weak base is so slightly modified in 0·01N-acid solution. More interesting is the fact that absorption falls to zero between 380 and 390 mμ and the characteristic, broad, long-wave-length maximum due to the ·N:N· group, already weak in cinnoline itself, disappears in this case.

The failure of 3-aminocinnoline to form a diazonium salt in dilute acid suggests the existence of resonance interaction between the amino-group and $N_{(2)}$ (IX) (Angyal and Angyal, *J.*, 1952, 1461), and this is in line with pK_a determinations and absorption spectra. The figures quoted above show that whilst 3-aminoquinoline and quinoline are almost identical in basic strength (Albert *et al.*, *loc. cit.*), 3-aminocinnoline is more basic by about

one pK unit than cinnoline (pK_a, 2·70). Although the base strengthening is smaller in this case than with 4-aminocinnoline and related compounds where it has been attributed to " additional ionic resonance " (Albert *et al.*, *loc. cit.*), yet the fact that the effect exists suggests that the cation of 3-aminocinnoline must be represented by (X), $N_{(2)}$ acting as the basic centre and permitting stabilisation by resonance as shown. The low degree of base strengthening in this case can be attributed to the incursion of an *o*-quinonoid form. The absorption spectra of 3-aminocinnoline (see Table) support the view that the proton in the cation is accepted by a ring-nitrogen atom, there being a bathochromic shift in acid solution. A hypsochromic shift of the broad, long-wave-length maximum occurs in alkali, as with the aminoquinolines (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). It is clearly desirable to decide the position of quaternisation of 3-aminocinnoline.

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374. *The Preparation of Bis-2-cyanoethyl Derivatives of Aromatic Primary Amines, and their Conversion into 1 : 6-Diketojulolidines. Part II.**

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

The cyanoethylation of aniline under the influence of various inorganic catalysts, and that of various aromatic primary amines under the influence of cuprous chloride, has been studied.

Several *NN*-bis-2-cyanoethylarylamines on cyclisation give the corresponding 2 : 6-diketojulolidines : others, however, undergo only monocyclisation, forming the corresponding *N*-2-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinolines.

p-Phenylenediamine very readily undergoes tetrakiscyanoethylation, and the product on cyclisation gives the red octahydro-1 : 10-diketophenanthroline (VII), which condenses with hydrazine to form the yellow hexahydrotetra-azapyrene (IX), the deep purple monomethiodide of which constitutes a new type of cyanine dye.

It has been shown (Braunholtz and Mann, Part I *) that several aromatic primary amines, when heated with vinyl cyanide and acetic acid, undergo mono- and/or bis-cyanoethylation, the latter being particularly favoured by acetic acid; *e.g.*, in formic acid, *p*-toluidine undergoes only monocyanoethylation. The utility of copper acetate, borate, or oleate or of cuprous chloride as additional catalysts for difficult cyanoethylations had already been proved (B.P. 457,621; R. C. Cookson and Mann, *J.*, 1949, 67). Smith and Tung-Yin Yu recently (*J. Amer. Chem. Soc.*, 1952, **74**, 1098) emphasised the value of cuprous chloride.

We have consequently investigated the cyanoethylation of aniline when boiled with vinyl cyanide and acetic acid in the presence of various metallic salts under comparable conditions, and find that ferrous sulphate, zinc acetate, and chromium trichloride afford only the monocyanoethyl derivative in 7, 13, and 55% yield, respectively, whereas cuprous cyanide, cobaltous chloride, and cuprous chloride give the biscyanoethyl derivative in 20, 30, and 55% yield, respectively. Smith and Tung-Yin Yu claim a 79% yield in the last case. (Throughout this paper the quoted yields of our cyanoethyl compounds are those of the once-recrystallised material. Our yields, moreover, are also comparable in that they were obtained throughout from one sample of vinyl cyanide: the yields given by different batches of the cyanide may vary according to the age of the cyanide and to the amount of stabiliser present.)

In view of the marked superiority of acetic acid containing cuprous chloride, we have investigated the cyanoethylation of a wider variety of primary aromatic amines when

* *J.*, 1952, 3046, is to be regarded as Part I.

heated under reflux with vinyl cyanide (2—2·5 mols.), acetic acid (2—2·5 mols.), and freshly prepared cuprous chloride (10 g. per mole of amine). The results are summarised in Table 1.

The yields of the biscyanoethyl derivatives, with the exception of that of *p*-anisidine, are uniformly greater than those recorded by Braunholtz and Mann (*loc. cit.*), who used acetic acid without the cuprous chloride but with heating in an autoclave at 140—145°. The yield of *NN*-bis-2-cyanoethylaniline claimed by Smith and Tung-Yin Yu (*loc. cit.*) was never achieved, our quoted yield being obtained consistently in several experiments. The preparation of *N*-2-cyanoethyl-*o*-toluidine, m. p. 108°, has been claimed (F.P. 47,827), but our product remained persistently as a mobile liquid: it is noteworthy, however, that acet-*o*-toluidide, m. p. 110°, was the major product in our attempted cyanoethylation of *o*-toluidine in an autoclave at 145—150° in the absence of cuprous chloride.

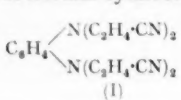
The influence in particular of two factors is apparent in Table 1. (*a*) A substituent *ortho* to the primary amino-group severely restricts formation of the biscyanoethyl derivative. Indeed, of such amines, only *o*-toluidine gave the dinitrile: α-naphthylamine, *o*-aminodiphenyl, *m*-2-xylidine, and mesidine gave none, and the last two (the only amines having two *o*-substituents) largely resisted cyanoethylation. This new example of the *ortho*-effect is presumably due to steric and not electronic causes, in view of the different substituents involved. (*b*) The low yields of cyanoethyl derivatives from *p*-chloroaniline and *p*-nitroaniline may indicate that, in the absence of other factors, cyanoethylation becomes more difficult as the basic strength of the amine falls. This does not accord with Whitmore, Mosher, Adams, Taylor, Chapin, Weisel, and Yanko's suggestion (*J. Amer. Chem. Soc.*, 1944, **66**, 725), based chiefly on their studies of aliphatic and heterocyclic amines, that cyanoethylation is governed more by the shape of the reacting molecules than by the basic strength of the amines.

TABLE 1.

Amine	Time of heating (hr.)	Mononitrile, $NHR{\cdot}C_2H_4{\cdot}CN$ Yield, %[b]	M. p.[a]	Dinitrile, $NR(C_2H_4{\cdot}CN)_2$ Yield, %[b]	M. p.[a]	Acetamido-compound: yield, %	Unchanged amine: yield, %
Aniline	12	—	—	55	83—84°	—	—
o-Toluidine	12	65	*	35	†	Trace	—
m-Toluidine	6	—	—	50	87—88	—	—
,,	12	—	—	65	,,	—	—
,,	20	—	—	75	,,	—	—
p-Toluidine	12	—	—	50	63—64	—	—
p-Anisidine	12	—	—	40	102—103	—	—
p-Chloroaniline	12	17	74·5—75·5°	20	95·5—96	—	—
p-Nitroaniline	12	*ca.* 6	128—130	—	—	—	22
α-Naphthylamine	10	80	70—71	—	—	—	—
β-Naphthylamine	12	—	—	25—35	127·5—128·5	—	—
o-$NH_2{\cdot}C_6H_4Ph$	12	65	86	—	—	—	—
p-$NH_2{\cdot}C_6H_4Ph$	12	—	—	80	165·5—166	—	—
1 : 2 : 4-$C_6H_3Me_2{\cdot}NH_2$	12	—	—	11	84	—	—
1 : 3 : 2-$C_6H_3Me_2{\cdot}NH_2$	12	—	—	—	—	*ca.* 50	*ca.* 20
1 : 3 : 5 : 2-$C_6H_2Me_3{\cdot}NH_2$	12	—	—	—	—	30	—

* Liquid, b. p. 125—126°/0·2 mm. † Liquid, b. p. 173°/0·2 mm.
[a] Of the pure compounds. [b] Of material once recrystallised.

Other more local factors may affect the yield. Our greater yield of the biscyanoethyl derivative of *p*-aminodiphenyl than of the analogous derivative of *p*-toluidine is probably due to the fact that the former derivative (unlike the latter) is almost insoluble in the reaction mixture, and its continuous separation would therefore prevent the attainment of the normal cyanoethylation equilibrium.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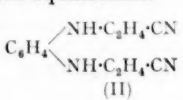
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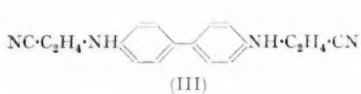

(III)

We have also investigated the cyanoethylation of certain aromatic diamines. *p*-Phenylenediamine underwent such ready cyanoethylation that no metallic catalyst was required: the diamine when heated at 120° with vinyl cyanide and acetic acid gave the

tetrakiscyanoethyl compound (I), m. p. 141—142°, in 85% yield, and a similar initial mixture when set aside at room temperature for 12 weeks gave this product in 76% yield. The identification of this compound required care, because the compositions of the diamine and its mono-, bis-, tris- and tetrakis-cyanoethyl derivatives are almost identical, and moreover it has been claimed (B.P. 613,807) that this process gives the *s-p*-biscyanoethyl compound (II), m. p. 140°. Our product, however, shows no >NH bands in the 3-μ region of its infra-red spectrum, and its cyclisation (described later) also shows conclusively that it is the tetracyano-derivative. In view of the very ready cyanoethylation of *p*-phenylenediamine, it is surprising that under similar conditions this diamine did not combine with α-methylacrylonitrile, ethyl acrylate, or ethyl cinnamate.

o-Phenylenediamine, when heated with vinyl cyanide and acetic acid, with or without cuprous chloride, gave only the *s-o*-biscyanoethyl compound (II), which was identified by (*a*) the presence of an >NH band in the 3-μ region of its spectrum, (*b*) formation of a nitrosamine which readily gave a Liebermann reaction, but no evidence of diazotisation or of green *p*-nitroso-derivative formation could be obtained. The effect of *ortho*-substituents in preventing biscyanoethylation of either amino-group is here again pronounced.

Benzidine, either with or without cuprous chloride, also gave solely the biscyanoethyl compound (III), the structure of which was determined by analysis and confirmed by the presence of the >NH band at 2·97 μ in its spectrum.

We have further investigated the cyclisation of certain of the above biscyanoethylamino-compounds. The conversion of bis-2-cyanoethylaniline into 1 : 6-diketojulolidine (IV; R = H) by the action of aluminium chloride in chlorobenzene containing hydrochloric acid has been improved, with the production of the pure diketone in 75% yield. *p*-Chloro-*NN*-bis-2-cyanoethylaniline gave, however, a monoketone, which is undoubtedly 6-chloro-1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline (V; R = Cl). The evidence for this structure is similar to that previously adduced (Braunholtz and Mann, *loc. cit.*) for the similar monoketone obtained from *NN*-bis-2-cyanoethyl-*p*-anisidine. The infra-red spectrum of the chloro-ketone shows well-defined bands at 4·45 and 6·00 μ corresponding to the −CN and the >CO groups respectively. Its ultra-violet spectrum is closely similar to that of the unsubstituted parent compound, 1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline and of the hydroxy- and the methoxy-ketone (V; R = HO and MeO) (cf. p. 1823) (Table 2).

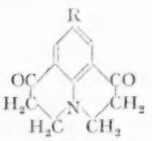
TABLE 2.

Compound		Absorption characteristics									
(V, R = Cl)	$\lambda_{max.}$	393	269	239			$\lambda_{min.}$	296	252		
	ε	4,490	11,270	25,500			ε	220	6,900		
Tetrahydro-4-keto-	$\lambda_{max.}$	377	259	235			$\lambda_{min.}$	286	251		
quinoline	ε	4,000	6,800	20,400			ε	48	5,900		
(V; R = HO)	$\lambda_{max.}$	410	264	239			$\lambda_{min.}$	297	259		
	ε	5,070	7,760	20,400			ε	100	7,460		
(V; R = MeO)	$\lambda_{max.}$	407	265	238			$\lambda_{min.}$	295	257		
	ε	5,100	8,080	28,800			ε	100	7,400		
(VI)	$\lambda_{max.}$	400	320	258	217		$\lambda_{min.}$	345	299	237	
	ε	6,700	5,700	36,500	25,200		ε	1,300	3,900	13,300	
[V; R = $(CN{\cdot}C_2H_4)_2N$]	$\lambda_{max.}$	424—431	277	247			$\lambda_{min.}$	321	267	216	
	ε	3,300	11,800	24,500			ε	180	10,900	7,900	
(I)	$\lambda_{max.}$	308—311	262				$\lambda_{min.}$	297	229—233		
	ε	1,860	17,600				ε	1,700	4,850		
Bis-2-cyanoethyl-*p*-	$\lambda_{max.}$	300	252				$\lambda_{min.}$	274	223		
toluidine	ε	1,900	15,800				ε	798	3,600		
VII)	$\lambda_{max.}$	492—496	248—251		$\lambda_{min.}$	382		220	$\lambda_{infl.}$	277—283	
	ε	5,500	19,400		ε	177		9,600	ε	8,100	
(IV; R = Me)	$\lambda_{max.}$	414—420	305	228	$\lambda_{min.}$	341		282	$\lambda_{infl.}$	256—260	
	ε	5,680	2,600	32,600	ε	314		1,050	ε	6,100	
(VIII)	$\lambda_{max.}$	478	322—325	252	238	215	$\lambda_{min.}$	375	288	245—247	222—224
	ε	4,500	2,500	22,000	22,900	19,400	ε	400	1,550	20,700	17,200

The above compounds are listed in the order in which they are mentioned in the text. All spectra were determined in ethanolic solution.

NN-Bis-2-cyanoethyl-β-naphthylamine similarly gave 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-keto-5 : 6-benzoquinoline (VI), the ultra-violet spectrum of which has some close

similarities to those of the above three monoketones (Table 2). *p-NN*-Bis-2-cyanoethylaminodiphenyl, however, gave 1 : 6-diketo-8-phenyljulolidine (IV; R = Ph). It is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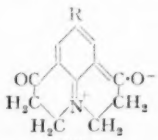
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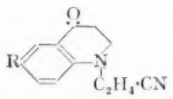
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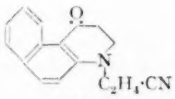
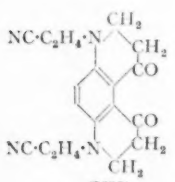

(VI)

characteristic of all the yellow diketo-julolidines of type (IV) that their ethanolic solutions become deep red on addition of hydrochloric acid. There is little doubt that these diketones exist as a resonance hybrid of (IV) and (IVA), the latter probably making the major contribution to the colour: salt formation involves essentially the addition of a proton to the negative oxygen atom in (IVA), this structure being thus almost exclusively formed (cf. Mann and Smith, *J.*, 1951, 1898).

The cyclisation of *NNN'N'*-tetrakis-2-cyanoethyl-*p*-phenylenediamine (I) is of particular interest. Mild conditions afford a brilliant yellow monoketone, which is almost certainly the analogue of our previous monoketones, *i.e.*, it is 1-2'-cyanoethyl-6-*NN*-bis-2-cyanoethylamino-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline [V; R = $(CN\cdot C_2H_4)_2N$], m. p. 149—150°, since its ultra-violet spectrum is again similar to that of the unsubstituted tetrahydro-4-ketoquinoline, but markedly different from that of the tetranitrile (I), which in turn closely resembles that of bis-2-cyanoethyl-*p*-toluidine (Table 2).

More vigorous conditions of cyclisation, however, give a beautiful vermilion diketone of composition $C_{18}H_{18}O_2N_4$ and m. p. 250—251°. This might be 4 : 7-bis-2'-cyanoethyl-1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-octahydro-1 : 10-diketo-4 : 7-phenanthroline (VII), the similar anthracene compound (VIII), or 8-*NN'*-di-(2-cyanoethyl)amino-1 : 6-diketojulolidine [IV; R = $(CN\cdot C_2H_4)_2N$]. Its identification as (VII) rests on the following evidence. (*a*) Its ultra-violet spectrum is entirely different from that of 1 : 6-diketo-8-methyljulolidine (IV; R = Me), which might reasonably be assumed to have a spectrum similar to that of [IV; R = $(CN\cdot C_2H_4)_2N$], particularly as the spectra of the *p*-toluidine dinitrile and tetranitrile (I) are so closely related. (*b*) The diketone reacts rapidly with hydrazine in hot methanolic solution to give the brilliant yellow 1 : 8-bis-2'-cyanoethyl-1 : 2 : 3 : 6 : 7 : 8-hexahydro-1 : 4 : 5 : 8-tetra-azapyrene (IX), a type of reaction which the two isomeric diketones could not give.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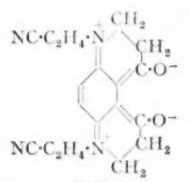
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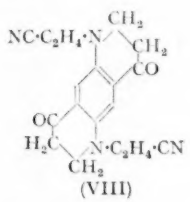
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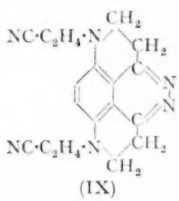
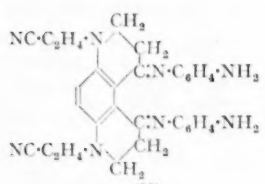
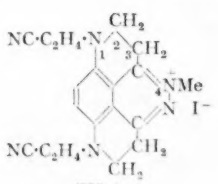
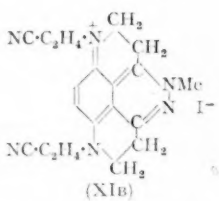

(IX)


(X)


(XIA)


(XIB)

We have attempted to prepare a compound analogous to (IX) by using *o*-phenylenediamine, but the only derivative isolated was the di-*o*-amino-anil (X): apparently the large-ring system which the condensation of one molecule of the diketone (VII) with one of the diamine would entail is too unstable for ready formation.

On one occasion the cyclisation of the tetranitrile (I) gave a brilliant orange diketone, m. p. 195—196°, isomeric with (VII). The minute yield precluded a detailed investigation, but its ultra-violet spectrum is entirely different from that of (VII), and, for example, from that of (IV; R = Me), and its infra-red spectrum shows the CN band at 4·44 μ and the >CO band at 5·95 μ, but the >NH band is absent from the 3-μ region: it is almost certain therefore that this diketone is the diaza-anthracenedione (VIII).

The colour of the red and of the orange diketone also supports the structures (VII) and (VIII), respectively. It is significant that in the red diketone (VII) charge separation can occur in either or in both amino-ketone rings as in (VIIA), but in the orange diketone (VIII), although this separation can occur in either amino-ketone ring, it cannot occur simultaneously in both: the greater degree of resonance in (VII) thus accounts for its deeper and more intense colour. In the monoketone [V; R = $(CN{\cdot}C_2H_4)_2N$] only one amino-ketone ring is involved, and the compound is thus yellow. It is probably not a coincidence that the m. p.s of the monoketone and of (VIII) and (VII) increase in this order, *i.e.*, as the possible proportion of polar component increases.

The yellow diazine (IX) is a compound of considerable interest. When added even to a large excess of methanolic picric acid solution, it formed a beautiful deep maroon, crystalline monopicrate, and a higher picrate could not be isolated. Similarly, even prolonged boiling of a mixture of (IX) with methyl iodide gave only a deep purple (almost black) crystalline monomethiodide, which gave a deep red ethanolic solution and also formed a reddish-purple methopicrate. It is clear therefore that the methyl iodide has caused quaternisation on the $N_{(4)}$ atom (XIA) and not the $N_{(1)}$ atom. Quaternisation on the $N_{(1)}$ atom should cause no significant change in the colour of the diazine, whereas that on the $N_{(4)}$ atom gives a cation which will exist as a resonance hybrid of (XIA) and (XIB). This explains the deep colour of the monopicrate and the monomethiodide, and the latter clearly represents an entirely new type of cyanine dye.

Experimental

Consistent m. p.s for certain compounds could only be obtained when determined in evacuated sealed tubes: these are denoted as "(E. T.)."

Cyanoethylation.—(A) *Aniline with inorganic catalysts.* In a series of experiments, mixtures of aniline (3·6 c.c.), vinyl cyanide (5·2 c.c., 2 mol.), acetic acid (2 c.c., 0·8 mol.), and various anhydrous inorganic catalysts (0·4 g.) were heated under reflux for 10 hr., and the mixture then cooled, made alkaline with saturated sodium carbonate solution, and extracted with chloroform. Evaporation of the extract and recrystallisation of the residue afforded mono-2-cyanoethylaniline from $FeSO_4$ (7% yield), $Zn(OAc)_2$ (15%), $CrCl_3$ (55%), and bis-2-cyanoethylaniline from $Cu_2(CN)_2$ (20%), $CoCl_2$ (30%), and Cu_2Cl_2 (55%). The yield in the last experiment was unchanged when the acetic acid was increased to 2·1 mol. The use of aluminium chloride led to a vigorous reaction in the cold solution, with production of a white aluminium derivative.

(B) *Various amines, with use of cuprous chloride.* In the experiments summarised in Table 1, a mixture of the amine, vinyl cyanide (2 mol.), acetic acid (2 mol.), and freshly prepared dry cuprous chloride (10 g. per g.-mol. of amine) was boiled under reflux for the time stated, cooled, and then vigorously stirred whilst an excess of concentrated ammonia solution was added. The precipitated oily nitrile usually slowly solidified and was then recrystallised: in the rare cases when solidification did not occur, the heavy oil was distilled. (Experimental details are given only when distillation was necessary.)

The solvent used for recrystallisation of the product was ethanol unless otherwise stated: the identity of known products was checked by mixed m. p. determinations. Aniline gave the dinitrile, m. p. 83—84°. *o*-Toluidine gave an oil which on distillation at 0·2 mm. gave fractions: (*a*) B. p. 67—75°, in very small amount: this was the acet-*o*-toluidide, and crystallised immediately after distillation. (*b*) B. p. 135—160°: this fraction when redistilled gave *N-2′-cyanoethyl-o-toluidine*, b. p. 125—126°/0·2 mm. (Found: C, 75·3; H, 7·3; N, 17·3. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5%). (*c*) B. p. 173°, which when redistilled gave *NN-bis-2′-cyanoethyl-o-toluidine*, b. p. 182°/0·4 mm. (Found: C, 72·9; H, 7·1; N, 19·5. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·0; N, 19·7%). These two nitriles were colourless liquids which could not be induced to crystallise. *m*-Toluidine gave the dinitrile, m. p. 86—87°: the increase in yield with time of heating is shown in Table 1. *p*-Toluidine and *p*-anisidine gave the dinitriles, m. p. 58—60° and 99—101°, respectively. *p*-Chloroaniline gave a product which

after recrystallisation was still a mixture, but on distillation at 0·5 mm. gave fractions: (*a*) b. p. 150—170°; (*b*) b. p. 170—195°; (*c*) b. p. 225°. Fractions (*a*) and (*b*) on recrystallisation gave *p*-chloro-*N*-2′-cyanoethylaniline, m. p. 74·5—75·5° (Found: N, 15·7. Calc. for $C_9H_9N_2Cl$: N, 15·5%): Bauer, Cymerman, and Sheldon (*J.*, 1951, 3312) give m. p. 76°. Fraction (*c*) gave the dinitrile, m. p. 95·5—96°. *p*-Nitroaniline gave a product which on cooling deposited the unchanged amine (22%). Treatment of the filtrate with ammonia then gave N-2′-*cyanoethyl*-p-*nitroaniline*, pale yellow needles (from ethanol or benzene), m. p. 128—130° (Found: C, 57·0, 57·0; H, 4·9, 4·9; N, 22·3. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·8; N, 22·0%). The infra-red spectrum showed the following significant groups: =NH at 3·04; $^-$CN at 4·43; $^-NO_2$ as a complex band at approx. 7·5 μ.

α-Naphthylamine gave a product which on distillation gave a fraction, b. p. 180—194°/0·2 mm.; this when recrystallised gave N-2′-*cyanoethyl*-α-*naphthylamine*, m. p. 70—71° (Found: C, 79·8; H, 6·5; N, 14·3. $C_{13}H_{12}N_2$ requires C, 79·6; H, 6·2; N, 14·3%). β-Naphthylamine gave NN-*bis*-2′-*cyanoethyl*-β-*naphthylamine*, m. p. 127·5—128·5° (Found: C, 77·1; H, 5·8; N, 16·9. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·0; N, 16·9%).

o-Aminodiphenyl gave o-N-2″-*cyanoethylaminodiphenyl*, m. p. 86° (from methanol) (Found: C, 81·0; H, 6·6; N, 12·7. $C_{15}H_{14}N_2$ requires C, 81·0; H, 6·4; N, 12·6%). *p*-Aminodiphenyl gave p-NN-*bis*-2″-*cyanoethylaminodiphenyl*, m. p. 165·5—166° (from acetone) (Found: C, 78·8; H, 6·5; N, 15·5. $C_{18}H_{17}N_3$ requires C, 78·6; H, 6·2; N, 15·3%).

o-4-Xylidine gave the NN-*bis*-2-*cyanoethyl* derivative, m. p. 84° (Found: C, 74·1; H, 7·3; N, 18·7. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%). *m*-2-Xylidine gave an oily product which on distillation at 0·3 mm. afforded the fractions: (*a*) b. p. 60—70°, mainly unchanged amine; (*b*) 125—130°, which solidified and gave the acetoxylidide, m. p. 177—178° (Found: N, 8·9. Calc. for $C_{10}H_{13}ON$: N, 8·6%); (*c*) b. p. 165—170°; the small amount precluded purification, but this fraction was apparently the 2-cyanoethyl derivative. Mesidine gave a product which on distillation afforded the acetyl derivative, m. p. 217·5—219·5° (Found: N, 8·0. Calc. for $C_{11}H_{15}ON$: N, 7·9%), most of the product forming an intractable gum in the distilling-flask.

In an earlier series of experiments in which cuprous chloride was not used, a mixture of *p*-aminobenzoic acid (19 g.), vinyl cyanide (27 c.c., 3 mol.), and acetic acid (22·5 c.c., 2·6 mol.) was heated in an autoclave at 150° for 7 hr., and on cooling deposited a pale yellow, granular solid (23 g.), which on fractional recrystallisation from ethanol yielded colourless crystals of p-(2-*cyanoethylamino*)*benzoic acid* (9·2 g., 35%), m. p. 221·5—222·5° (Found: C, 63·1; H, 5·1; N, 14·8. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·7%). The more soluble fractions yielded only *p*-acetamidobenzoic acid, m. p. 255—256° (decomp.) (Found: N, 8·0. Calc. for $C_9H_9O_3N$: N, 7·8%). This result again exemplifies the fact that weak bases undergo cyanoethylation with difficulty and seldom beyond the mononitrile stage.

o-Toluidine, when treated under the same conditions as the above acid, gave acet-*o*-toluidide, m. p. 111—112° (Found: N, 9·35. Calc. for $C_9H_{11}ON$: N, 9·4%), with a trace of a higher-boiling liquid fraction.

(C) *Diamines.* (i) *p*-Phenylenediamine. (*a*) A series of experiments showed that the highest yield of the tetranitrile was obtained when the diamine was heated with vinyl cyanide (5·4 mol.) and acetic acid (4·2 mol.) in a sealed tube at 120° for 14 hr. On cooling, NNN′N′-*tetrakis*-2′-*cyanoethyl*-p-*phenylenediamine* (I) (83%) crystallised in colourless needles, m. p. 132—136°, raised to 141—142° by recrystallisation from ethanol (Found: C, 67·2; H, 6·3; N, 26·1. $C_{18}H_{20}N_6$ requires C, 67·5; H, 6·3; N, 26·2%). (*b*) When a mixture of the amine, vinyl cyanide (7·7 mol.), and acetic acid (4·2 mol.) was boiled under reflux for 24 hr., the yield of (I) was 70%. (*c*) When a mixture identical with that in (*b*) was first gently warmed to give a clear solution and then set aside in a securely closed flask for 12 weeks, the yield of (I) was 76%.

An acetone solution of (I) was saturated with hydrogen chloride, and the precipitated white *dihydrochloride*, m. p. 160—161°, then collected, washed with acetone, and dried in desiccator (Found: C, 54·5; H, 5·9; N, 21·0. $C_{18}H_{20}N_6,2HCl$ requires C, 54·9; H, 5·6; N, 21·3%). The salt is unstable in moist air and readily deposits the free base.

When a mixture of the diamine and acetic acid was heated with α-methylacrylonitrile (with or without cuprous chloride) or with ethyl cinnamate, the chief product was *NN*′-diacetyl-*p*-phenylenediamine, whereas use of ethyl acrylate gave a brown gum.

(ii) *o*-Phenylenediamine. A mixture of the diamine, vinyl cyanide (8 mol.), and acetic acid (4·2 mol.) was boiled under reflux for 24 hr., and the cold reaction mixture made alkaline and then extracted with ether. After evaporation of the solvent, the residue when recrystallised from methanol gave NN′-*bis*-2′-*cyanoethyl*-o-*phenylenediamine* (II) as colourless crystals,

m. p. 118·5—119° (Found: C, 67·4; H, 6·3; N, 26·4. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·6; N, 26·2%). In all subsequent preparations, the dinitrile (II) crystallised as the reaction mixture cooled.

(iii) Benzidine. When a mixture of benzidine, vinyl cyanide (8 mol.), and acetic acid (4·5 mol.) was boiled under reflux for 8 hr., *NN'-bis-2''-cyanoethylbenzidine* (III) separated in quantitative yield from the hot mixture: after cooling, it was collected and recrystallised from 2-methoxyethanol, giving colourless crystals, m. p. 245—245·5° (Found: C, 74·4; H, 6·3; N, 19·2. $C_{18}H_{18}N_4$ requires C, 74·4; H, 6·3; N, 19·3%). Attempts further to cyanoethylate the dinitrile (III) gave intractable gums.

Cyclisation.—Bis-2'-cyanoethylaniline. Consistent yields of pure 1 : 6-diketojulolidine, m. p. 145—146° (75%), are obtained by the method previously described (Braunholtz and Mann, *loc. cit.*) if the reaction mixture is heated to 170° (oil-bath temp.) for 8·5 hr., allowed to cool, then poured cautiously into ice-water and worked up as before. The diketone readily gives a *bis-diphenylhydrazone*, intensely yellow crystals (after washing with methanol), m. p. 210—211° (Found: C, 81·2; H, 5·8; N, 12·9. $C_{36}H_{31}N_5$ requires C, 81·0; H, 5·9; N, 13·1%).

p-*Chloro*-NN-*bis-2'-cyanoethylaniline.* This dinitrile (5 g.) was added to a mixture of chlorobenzene (15 c.c.), aluminium chloride (25 g., 8·75 mol.), and concentrated hydrochloric acid (1 c.c.), which was heated with stirring at 155° for 8 hr. After cooling, hydrolysis by ice-water, and removal of chlorobenzene by steam-distillation, a viscous reddish-brown tar slowly separated in the residue. An ethanolic solution of this tar deposited the crystalline yellow *6-chloro-1-2'-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline* (V; R = Cl) (2 g., 40%), m. p. 136—137° (from ethanol) (Found: C, 61·3; H, 4·9; N, 12·2. $C_{12}H_{11}ON_2Cl$ requires C, 61·3; H, 4·7; N, 11·9%). It formed a *semicarbazone*, yellow needles (from aqueous ethanol), m. p. 173—175° (Found: C, 53·4; H, 5·1; N, 23·8. $C_{13}H_{14}ON_5Cl$ requires C, 53·5; H, 4·8; N, 24·0%).

NN-*Bis-2'-cyanoethyl*-p-*anisidine.* This dinitrile, when treated as the above bis-2'-cyanoethylaniline, gave, after removal of the chlorobenzene, a heavy oil which separated from the cold mixture and slowly solidified. Recrystallisation from ethanol gave *6-hydroxy-1-2'-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline* (V; R = HO) (18%), bright orange crystals, m. p. 176—177° (Found: C, 66·5; H, 5·5; N, 12·9. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 12·95%); this gave a *2 : 4-dinitrophenylhydrazone*, dark purple crystals, m. p. 250° (decomp.) (Found: C, 53·5; H, 4·4; N, 20·7. $C_{18}H_{16}O_5N_6,\frac{1}{2}H_2O$ requires C, 53·3; H, 4·2; N, 20·7%), which became anhydrous at 75°/0·1 mm. (Found: C, 54·5; H, 3·9. $C_{18}H_{16}O_5N_6$ requires C, 54·55; H, 4·05%).

The ketone (V; R = HO) readily gave a bright red solution in 10% aqueous sodium hydroxide, and its aqueous ethanolic solution gave a purple-brown colour with ferric chloride.

That demethylation had accompanied the above cyclisation was confirmed as follows: (*a*) the ketone in alkaline solution with methyl sulphate gave *6-methoxy-1-2'-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline* (V; R = MeO), yellow crystals (from ethanol), m. p. 122—123° (Found: C, 67·75; H, 6·4; N, 12·1. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·15; N, 12·15%) [*2 : 4-dinitrophenylhydrazone*, deep purple, m. p. 231° (decomp.) (Found: N, 20·3. $C_{19}H_{18}O_5N_6$ requires N, 20·45%); (*b*) the ketone when similarly treated with benzoyl chloride gave *6-benzoyloxy-1-2'-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-ketoquinoline* (V; R = BzO), pale yellow (from ethanol), m. p. 149—150° (Found: C, 71·6; H, 5·2; N, 8·8. $C_{19}H_{16}O_3N_2$ requires C, 71·3; H, 5·05; N, 8·75%).

In Part I (*loc. cit.*), the above hydroxy-compound, m. p. 176—177°, was isolated in very small quantity and erroneously identified as the methoxy-compound. The compound prepared above has the same m. p. (mixed and unmixed) and the same absorption spectrum as our earlier compound, and its identity is now certain. This mistaken identity does not affect the validity of our earlier evidence for the structure of the monoketone ring.

NN-*Bis-2'-cyanoethyl-β-naphthylamine.* This dinitrile, treated at 170° as above, gave a heavy brown oil which slowly solidified. An extract in boiling benzene on cooling deposited *1-2'-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-keto-5 : 6-benzoquinoline* (VI) (82%), which, recrystallised from ethanol, gave bright yellow crystals, m. p. 121·5—123·5° (Found: C, 76·6; H, 5·5; N, 11·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). It gave a *semicarbazone*, pale yellow needles (from aqueous ethanol), m. p. 233° (Found: C, 66·7; H, 5·8; N, 22·7. $C_{17}H_{17}ON_5$ requires C, 66·5; H, 5·6; N, 22·8%).

p-NN-*Bis-2''-cyanoethylaminodiphenyl.* This dinitrile, treated as above, gave on hydrolysis a brilliant scarlet suspension, which, however, when steam-distilled to remove chlorobenzene, changed colour and deposited the solid granular *1 : 6-diketo-8-phenyljulolidine* (IV; R = Ph) (85%); after recrystallisation from methanolic acetone, this afforded lustrous yellow crystals,

m. p. 228·5—229·5° (Found : C, 77·8; H, 5·4; N, 5·1. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·45; N, 5·1%). It gave a *bisphenylhydrazone*, m. p. 239—240° (E.T.), after being washed with warm methanol and dried at 50°/0·1 mm. (Found : C, 78·5; H, 6·0; N, 15·0. $C_{30}H_{27}N_5$ requires C, 78·75; H, 5·95; N, 15·3%).

NNN'N'-*Tetrakis*-2'-*cyanoethyl*-p-*phenylenediamine* (I). A considerable variation in the conditions employed for this cyclisation was studied, and the following are apparently the optimum conditions for the formation of the mono- and the di-ketone. The course of the reaction is apparently determined less by the time of heating and proportion of aluminium chloride than by the temperature : oil-bath temperatures of 160—165° favour monoketone formation, but those of *ca.* 175° give solely the diketone.

(*a*) The tetranitrile (5 g.) was added to a mixture of chlorobenzene (70 c.c.), aluminium chloride (70 g., 25 mol.), and concentrated hydrochloric acid (3 c.c.), which was then kept at 160° with vigorous stirring for 20 hr. It was cooled, hydrolysed with ice-water, and steam-distilled to remove chlorobenzene as before The cold residual liquid contained a small amount of dark tar, from which no pure component could be isolated. The dark red supernatant aqueous layer was therefore extracted with chloroform, and the dried extract (which was deep red with an orange fluorescence) on evaporation left a red gum. The latter on recrystallisation from methanol gave brilliant yellow crystals of 1-2'-*cyanoethyl*-6-NN-*bis*-(2-*cyanoethyl*)*amino*-1 : 2 : 3 : 4-*tetrahydro*-4-*ketoquinoline* [V; R = $(CN{\cdot}C_2H_4)_2N$], m. p. 149—150° (0·5 g., 10%) (Found : C, 67·4; H, 6·0; N, 22·0. $C_{18}H_{19}ON_5$ requires C, 67·3; H, 6·0; N, 21·8%). It formed a *semicarbazone*, yellow crystals (from aqueous ethanol), m. p. 206—207° (Found : N, 29·6. $C_{19}H_{22}ON_8$ requires N, 29·6%).

(*b*) A mixture of the tetranitrile (5 g.) with chlorobenzene (40 c.c.), aluminium chloride (41 g., 14·5 mol.), and concentrated hydrochloric acid (2 c.c.) was heated at 175° for 10 hr. and then treated as above. Evaporation of the chloroform gave a red gum which on recrystallisation from methanol afforded vermilion needles of 4 : 7-*bis*-2'-*cyanoethyl*-1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*octahydro*-1 : 10-*diketo*-4 : 7-*phenanthroline* (VII), m. p. 250—251° (E.T.) (0·25 g., 5%) (Found : C, 67·3; H, 5·7; N, 17·6, 17·5. $C_{18}H_{18}O_2N_4$ requires C, 67·1; H, 5·6; N, 17·4%).

(*c*) On one occasion when the tetranitrile (10 g.) was heated with chlorobenzene (100 c.c.), aluminium chloride (125 g., 22 mol.), and hydrochloric acid (3 c.c.) at 160—165° for 30 hr., and then worked up as before, repeated recrystallisation of the residual gum from methanolic acetone gave brilliant orange plates, m. p. 195—196°, of the isomeric diketone, presumably 1 : 5-*bis*-2'-*cyanoethyl*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*octahydro*-1 : 5-*diaza*-*anthracene*-4 : 8-*dione* (VIII) (Found : C, 67·5; H, 5·9; N, 17·0. $C_{18}H_{18}O_2N_4$ requires C, 67·1; H, 5·6; N, 17·4%) : mixed m. p. with (VII), 185·5—199·5°. In solution this compound gave a 2 : 4-dinitrophenylhydrazone.

All attempts to cyclise the tetranitrile (I) by means of aluminium chloride in ethylene dichloride or in nitrobenzene, or of ferric or stannic chloride failed.

Derivatives of the diketone (VII). (*a*) When an excess of hydrazine hydrate was added to a hot methanolic solution of (VII), the bright red colour changed immediately to bright yellow, and 1 : 8-*bis*-2'-*cyanoethyl*-1 : 2 : 3 : 6 : 7 : 8-*hexahydro*-1 : 4 : 5 : 8-*tetra*-*azapyrene* (IX) separated in almost theoretical yield as yellow needles, m. p. 271—272° (E.T.) (from methanol) (Found : C, 67·85; H, 5·6; N, 26·6. $C_{18}H_{18}N_8$ requires C, 67·8; H, 5·7; N, 26·4%). It formed from ethanol a deep maroon *monopicrate*, m. p. 223·5° (decomp., E.T.) (Found : C, 52·6; H, 4·0; N, 22·7. $C_{18}H_{18}N_8{,}C_6H_3O_7N_3$ requires C, 52·6; H, 3·9; N, 23·0%).

When a fine suspension of (VII) in methyl iodide was boiled under reflux for 6 hr., the deep purple *monomethiodide* (XIA or B) separated, m. p. 190—191° (decomp.) after recrystallisation from ethanol (Found : C, 49·6; H, 4·7; N, 18·25. $C_{19}H_{21}N_6I$ requires C, 49·6; H, 4·6; N, 18·25%). It formed a *monomethopicrate*, reddish-purple plates, m. p. 130·5—131·5° (decomp.) (Found : C, 53·5; H, 3·95; N, 22·2. $C_{25}H_{23}O_7N_9$ requires C, 53·5; H, 4·1; N, 22·45%).

(*b*) A solution of the diketone (VII) (0·075 g.) and *o*-phenylenediamine (0·075 g., 3 mol.) in acetic acid (5 c.c.) was boiled under reflux for 1·5 hr., becoming almost colourless. The cold solution was poured into water, which when basified deposited in small yield the *di*-o-*amino*-*anil* (X) of the diketone : repeated recrystallisation from benzene–*cyclo*hexane gave colourless crystals, m. p. 175·5—176·5° (Found : C, 71·7; H, 5·8; N, 22·2. $C_{30}H_{30}N_8$ requires C, 71·7; H, 6·0; N, 22·3%). When the above condensation was repeated with the diamine (1 mol.) and 4 hours' heating, no definite product could be isolated.

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375. *An Alkaloid of* Dioscorea hispida, *Dennstedt. Part II.* Hofmann Degradation.*

By A. R. Pinder.

Further investigations relating to the constitution of the alkaloid from *Dioscorea hispida*, Dennst., are described. Hofmann degradation of the alkaloid has given an unsaturated, oxygen-free base, $C_{13}H_{21}N$, which has three double bonds, but is not aromatic. Additional chemical and pharmacological evidence supporting the view that the alkaloid is identical with dioscorine is recorded.

Investigations described in Part I * (see also *Nature*, 1951, **168**, 1090) have shown that the alkaloid occurring in the tubers of *Dioscorea hispida*, Dennst., contains an αβ-unsaturated six- or higher-membered lactone ring. In addition, chemical and botanical evidence was presented supporting the view, previously expressed by Leyva and Gutierrez (*J. Philippine Is. Med. Assoc.*, 1937, **17**, 349) on the basis of colour reactions and toxicological properties, that the alkaloid is identical with dioscorine, obtained by Schütte (*Nederl. Tijdschr. Pharm.*, 1897, **9**, 131) and Gorter (*Rec. Trav. chim.*, 1911, **30**, 161) from the tubers of *Dioscorea hirsuta*, Blume.

Additional chemical evidence supporting the belief that the base from *D. hispida* is dioscorine is now submitted. Hofmann degradation of the alkaloid from *D. hispida* gave two products, in approximately equal yield. The lower-boiling product was an oxygen-free base, characterised as the methiodide and picrate. Analyses supported the formula $C_{13}H_{21}N$ for the base, which is in agreement with the formula of the base obtained by Gorter (*loc. cit.*) by the Hofmann degradation of dioscorine. The properties of the two Hofmann bases are in agreement, except that Gorter's amine is reported as having an aniline-like odour, whereas the base obtained in this laboratory has an odour typical of an aliphatic or alicyclic amine.

The higher-boiling product was mainly the unchanged alkaloid, formed by elimination of methanol from the methohydroxide, but there was evidence that this fraction contained a small proportion of a more unsaturated compound, as in addition to the maximum in the ultra-violet absorption spectrum at 2170 Å, characteristic of the alkaloid (see Part I), there was a maximum at 2650 Å ($\varepsilon = 1700$), which suggests the presence of a diene system conjugated with a carbonyl group (Braude, *Ann. Reports*, 1945, **42**, 105). Such a grouping would almost certainly be found in the normal methine base of the alkaloid.

The base $C_{13}H_{21}N$ is evidently the result of deep-seated decomposition of the methohydroxide of the alkaloid, and the presence of the nitrogen atom indicates that in the alkaloid this atom is part of a heterocyclic ring. The elimination of the lactone ring recalls Boekelheide and Agnello's recent finding (*J. Amer. Chem. Soc.*, 1951, **73**, 2286) that the lactonic alkaloid β-erythroidine, when converted into its dihydro-derivative and subjected to Hofmann degradation, furnished an oxygen-free base as well as the normal methine base. The base $C_{13}H_{21}N$ is formed by the loss of water and carbon dioxide from the methohydroxide; if it be assumed that one double bond is formed for the elimination of each of these simple molecules, the base may be expected to contain three ethylenic linkages. That this was the case was proved by catalytic hydrogenation of the base under mild conditions, using a pre-reduced catalyst. Three mols. of hydrogen were absorbed, with the formation of a saturated hexahydro-base $C_{13}H_{27}N$, characterised as the methiodide. It may be concluded that the three double bonds are not present as a benzene ring; in confirmation ozonolysis of the base gave formaldehyde in high yield, indicating the presence of a terminal methylene group. The infra-red absorption spectrum of the base (bands at 3·23, 5·80, and 11·26 μ) is consistent with this. In addition, bands at 5·61 and 5·73 μ, and the absence of strong bands between 10 and 11 μ, suggest that this grouping is of the type $\begin{matrix}C\\C\end{matrix}\!>\!C\!:\!CH_2$ rather than $CH\!:\!CH_2$ (Thompson, *J.*, 1948, 328; Williams, *Rev. Sci. Instr.*, 1948, **19**, 143; cf. Boekelheide, Grundon, and Weinstock, *J. Amer. Chem. Soc.*,

* Part I, *J.*, 1952, 2236.

1952, **74**, 1866). All these bands are absent from the spectrum of the hexahydro-base $C_{13}H_{27}N$.

The ultra-violet absorption curve of the base $C_{13}H_{21}N$ shows a single wide maximum at 2700 Å ($\varepsilon = 17{,}500$), which suggests that the three double bonds of the base are conjugated. Cases for comparison include *cyclo*octa-1 : 3 : 5-triene [max. at 2650 Å ($\varepsilon = 3715$) (Cope and Overberger, *J. Amer. Chem. Soc.*, 1948, **70**, 1433; Cope, Nace, and Estes, *ibid.*, 1950, **72**, 1123)], octa-2 : 4 : 6-triene [max. at 2600 Å ($\varepsilon = 7940$) (Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones, and Coenzymes," Adam Hilger, Ltd., London, 2nd Edn., 1942, p. 25)], and octa-2 : 4 : 6-trien-1-ol [max. at 2645 Å ($\varepsilon = 53{,}000$) (von Euler, Karrer, Klussman, and Morf, *Helv. Chim. Acta*, 1932, **15**, 502)]. The width of the maximum and the low melting point (120—122°) of the methiodide of the base suggest that the base is probably a mixture of conjugated trienes, arising because of the unsymmetrical placing of the nitrogen atom, especially with respect to the lactone ring, so that the elements of water may be eliminated from the methohydroxide in different ways. It is unlikely that in any of these structures for the base $C_{13}H_{21}N$ the nitrogen atom is attached to the chromophoric system since a nitrogen atom so placed is associated with a large bathochromic effect (*e.g.*, buta-1 : 3-diene, $\lambda_{max.}$ 2190 Å; 1-diethylaminobuta-1 : 3-diene, $\lambda_{max.}$ 2810 Å; Braude, *loc. cit.*).

The hexahydro-base $C_{13}H_{27}N$ forms a methiodide, m. p. 182—183°, but it has not so far been possible to establish whether this base is homogeneous. The infra-red absorption spectrum of the base shows a wide band of medium intensity at 11·75—12·1 μ, which suggests the presence of a trimethylene group (Thompson, *loc. cit.*).

Investigations of the structure of the two bases are being continued. If it can be assumed that the base $C_{13}H_{21}N$ is identical with that obtained by Gorter, it seems likely that it is a mixture of alkenyldimethylamino*cyclo*heptadienes, since Gorter (*loc. cit.*) reported the conversion of the base, by further Hofmann degradation, hydrobromination, dehydrobromination, and oxidation, into *o*-toluic acid.

Reduction of the dihydro-alkaloid with lithium aluminium hydride gave a syrupy glycol-base, with a strong band in the infra-red at 3·0 μ, characteristic of the hydroxyl group.

Extraction of tubers of *D. hispida* according to the procedure of Marker and his coworkers (*J. Amer. Chem. Soc.*, 1940, **62**, 2542; 1942, **64**, 1283) failed to yield sapogenins. It has also been established that the tubers of *Dioscorea macrostachia* and of *D. composita* (kindly supplied by Professor Carl Djerassi, late of Syntex, S.A., Mexico) do not contain any alkaloidal material.

Pharmacology.—The author is grateful to Mr. A. F. Green of the Wellcome Research Laboratories for the following pharmacological report.

Analeptic and convulsant actions were shown when the alkaloid was given in large doses. The duration of anæsthesia of mice under pentobarbitone sodium was shortened by 50 mg./kg. given intravenously, but less than by 1—2 mg./kg. of picrotoxin. In anæsthetised mice convulsions occurred with 50 mg./kg., and 100 mg./kg. were usually fatal. It was also found that 20 mg./kg. intravenously increased the breathing and lightened the degree of anæsthesia in a cat under pentobarbitone sodium. No other actions of importance were found. Intraperitoneally in mice the LD_{50} was about 120 mg./kg. There was no analgesic effect with large doses in rats. Concentrations of $1 : 10^{-5}$ did not affect the movement of the isolated guinea-pig or rabbit ileum, or their responses to acetylcholine and histamine. The cat blood pressure was hardly affected by 20 mg./kg. intravenously, and its responses to acetylcholine, histamine, adrenaline, and noradrenaline were not influenced. Mydriatic activity could not be demonstrated either by direct application of a 0·1% solution to the eyes of mice or by intraperitoneal injection of as much as 50 mg./kg. Atropine under these conditions is active in 0·0005% solution or at 0·05 mg./kg. The alkaloid caused mydriasis only at toxic doses. The dihydro-alkaloid showed no pharmacological effects.

The properties of the alkaloid described above are in general similar to those of dioscorine, which have been reported earlier somewhat scantily. Thus Schütte (*loc. cit.*) reported that dioscorine had picrotoxin-like properties and Gorter (*loc. cit.*) confirmed this,

noting that large doses were required. Leyva and Gutierrez (*loc. cit.*) noted similar toxicological effects with the alkaloid of *D. hispida*, but unfortunately their finding that a monkey dying after a large dose of the alkaloid had dilated pupils has been misused as evidence for a mydriatic effect, resembling that of tropine, when it might have been better regarded as due to asphyxia or some other agonal effect. There are therefore no pharmacological data to indicate that the alkaloid of *D. hispida* investigated in this laboratory is different from dioscorine itself.

Experimental

Most of the analyses are by Mr. F. C. Hall. Spectral measurements are by Dr. F. B. Strauss, with the assistance of Mr. F. Hastings.

Hofman Degradation of the Alkaloid.—The crystalline alkaloid (2·0 g.) in dry methanol (10 c.c.) and methyl iodide (5 c.c.) were refluxed on the water-bath for 3 hr. After removal of the solvent and excess of methyl iodide *in vacuo* the residual crystalline methiodide (3·3 g., 100%) was dissolved in water (15 c.c.) and the solution treated with freshly precipitated silver oxide, prepared from silver nitrate (3·0 g.) and N-sodium hydroxide (50 c.c.). After 12 hr. with occasional shaking the solution was filtered and the filtrate evaporated to dryness *in vacuo* on the water-bath. The foamy methohydroxide (2·1 g.) so obtained decomposed smoothly at 180—220°/12 mm., giving an aqueous distillate (1·4 g.), which was heated under reflux on the water-bath with 20% aqueous potassium hydroxide (20 c.c.) for 1 hr. The cooled solution was extracted several times with ether, and the combined extracts were dried (KOH). Removal of the ether through a short Vigreux column gave an oily base, which distilled at 125° (bath)/8 mm. (0·6 g.) and had $[\alpha]_D^{18}$ −185° (*c*, 1·0 in $CHCl_3$) (Found: C, 81·9; H, 11·25; N, 7·55; CMe, 6·0. Calc. for $C_{13}H_{21}N$: C, 81·7; H, 11·0; N, 7·3; 1*C*-Me, 7·85%). Gorter (*loc. cit.*) reports b. p. of Hofmann base from dioscorine 116—120°/8 mm. Ultra-violet absorption in ethanol: Max. at 2700 Å, ε = 17,500. Infra-red absorption (liquid film): Bands at 3·23, 5·61, 5·73, 5·80, 6·11, and 11·26 μ.

A *methiodide* was obtained by refluxing the Hofmann base (0·1 g.) with methyl iodide (2 c.c.) for 10 min.; it separated from ethanol–ether in clusters of glistening prisms, m. p. 120—122° (Found: C, 50·2; H, 7·0; I, 38·0. $C_{14}H_{24}NI$ requires C, 50·45; H, 7·2; I, 38·1%). A *picrate*, prepared in the usual manner in methanol, separated from methanol in rhombic prisms, m. p. 129—130° (Found: C, 54·5; H, 5·6. $C_{19}H_{24}O_7N_4$ requires C, 54·3; H, 5·7%).

Acidification of the potassium hydroxide solution above, followed by basification with sodium carbonate and extraction with chloroform, gave a base distilling at 140—150° (bath)/0·06 mm. (0·7 g.), which was mainly unchanged alkaloid (picrate, m. p. and mixed m. p. 187°), but the appearance in the ultra-violet absorption spectrum of a peak at 2650 Å (ε = 1,700) indicates that the product contains some of the normal methine base of the alkaloid.

Ozonolysis of the Base $C_{13}H_{21}N$.—A solution of the base $C_{13}H_{21}N$ (0·25 g.) in purified chloroform (20 c.c.) was ozonised at room temperature for 3 hr. Evaporation of the solvent *in vacuo* at room temperature gave an oily ozonide, which was decomposed by distillation with normal hydrochloric acid (50 c.c.), about 40 c.c. of distillate being collected. The distillate, with an excess of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, gave formaldehyde 2 : 4-dinitrophenylhydrazone, yellow needles (from ethanol) (0·20 g.), m. p. and mixed m. p. 160—161°.

Catalytic Hydrogenation of the Base $C_{13}H_{21}N$.—Adams' platinum oxide catalyst (*ca.* 50 mg.) was suspended in N-hydrochloric acid (10 c.c.) and pre-reduced by shaking in hydrogen at room temperature and pressure for 30 min. A solution of the base $C_{13}H_{21}N$ (0·20 g.) in N-hydrochloric acid (10 c.c.) was then added and the shaking resumed. After 1 hr. absorption had ceased (at 17°/760 mm., 78 c.c.; calc. for $3H_2$, 77 c.c.). The solution was filtered and basified with potassium hydroxide, and the product isolated with ether. The dried ethereal solution was evaporated through a short Vigreux column, and the residual oily *base* distilled, b. p. 125—128° (bath)/12 mm., 110° (bath)/9—10 mm. (0·20 g.), $[\alpha]_D^{19}$ −36·7° (*c*, 1·5 in $CHCl_3$) (Found: C, 79·1; H, 13·9; N, 7·1; CMe, 6·55, 7·05. $C_{13}H_{27}N$ requires C, 79·2; H, 13·7; N, 7·1; 1*C*-Me, 7·6%). The base did not decolorise dilute, aqueous permanganate at room temperature in 30 sec. Infra-red absorption (liquid film): Band of medium intensity at 11·75—12·1 μ.

A *methiodide* was obtained by refluxing the base (0·1 g.) with methyl iodide (2 c.c.) for 10 min.; evaporation of volatile matter furnished a syrup, which crystallised on trituration with acetone. The salt separated from the same solvent in clusters of elongated prisms, m. p. 182—183° (Found, on material dried at 100° *in vacuo*: C, 49·9; H, 8·8; I, 37·4. $C_{14}H_{30}NI$ requires C, 49·6; H, 8·8; I, 37·5%).

Lithium Aluminium Hydride Reduction of the Dihydro-alkaloid.—The dihydro-alkaloid, obtained as described previously, had $[\alpha]_D^{20}$ 0° (*c*, 3·1 in $CHCl_3$) and its syrupy *hydrochloride* had $[\alpha]_D^{26}$ +20° (*c*, 1·8 in H_2O). The dihydro-base (1·0 g.) in dry ether (50 c.c.) was slowly added with shaking to a suspension of powdered lithium aluminium hydride (0·7 g.) in dry ether (75 c.c.) during 20 min. After 3 hr. the mixture was refluxed on the water-bath for a further 2 hr., then decomposed with moist ether with ice-cooling and with " Celite 545 " as coagulant. Water (20 c.c.) was added, followed by 30% aqueous potassium hydroxide (100 c.c.). The mixture was then subjected to continuous ether-extraction for 16 hr. The dried extract was evaporated and the syrupy basic *glycol* distilled [b. p. 155—160° (bath)/0·01 mm.; 0·9 g.] (Found: C, 69·0; H, 11·1. $C_{13}H_{25}O_2N$ requires C, 68·7; H, 11·0%). The product was a colourless, viscous liquid, very soluble in water. Infra-red absorption (liquid film): Strong band at 3·0 μ.

A *picrate*, prepared in the usual manner in methanol, separated from the same solvent in clusters of yellow prisms, m. p. 140—144°, with previous softening at 137° (Found, on material dried at 80° *in vacuo*: C, 50·3; H, 6·1. $C_{19}H_{28}O_9N_4$ requires C, 50·0; H, 6·1%).

The author thanks Professor Sir Robert Robinson, O.M., F.R.S., for his continued interest, and Dr. H. R. Ing, F.R.S., for his advice. Grateful acknowledgment is made to the Chemical Society for a grant towards the cost of the investigations, to Professor Sir John Simonsen, F.R.S. (Colonial Products Research Council) and Professor R. A. Robinson (University of Malaya) for gifts of *D. hispida* tubers, and to Messrs. T. and H. Smith, Ltd., for assistance with the extraction of the tubers. The work was carried out during the tenure of a Pressed Steel Company Research Fellowship in the University of Oxford.

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376. *Constituents of* Filix Mas. *Part III.* Albaspidin.*

By A. MCGOOKIN, ALEXANDER ROBERTSON, and T. H. SIMPSON.

The structure (II) for flavaspidic acid is substantiated by disproportionation to give albaspidin (III) and by synthesis.

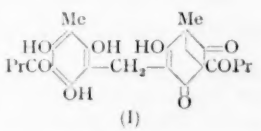
FOR flavaspidic acid, a constituent of male-fern extract, Boehm (*Annalen*, 1901, **318**, 230) preferred the structure (I) based on the empirical formula $C_{24}H_{28}O_8$ rather than (II) $C_{24}H_{30}O_8$ because on hydrolytic fission with alkalis and zinc dust the compound gave rise to *C*-trimethylphloroglucinol in addition to the fission products expected on the basis of structure (II), *viz.*, *C*-methyl- and *CC*-dimethyl-phloroglucinol, filicinic acid (V; R = H), and *n*-butyric acid. In a re-examination of flavaspidic acid the analytical results obtained, as well as those of Boehm (*loc. cit.*), were found to be in closer agreement with the empirical formula $C_{24}H_{30}O_8$ than with $C_{24}H_{28}O_8$ and, further, with hot aqueous sodium carbonate in the absence of a reducing agent (*e.g.*, zinc) flavaspidic acid readily disproportionated to give albaspidin (III), identical with synthetical material; thus, as in formula (II), the compound contains the normal filicinic acid residue (V; R = H). The second expected symmetrical disproportionation product, 5 : 5′-di-*n*-butyryl-2 : 4 : 6 : 2′ : 4′ : 6′-hexahydroxy-3 : 3′-dimethyldiphenylmethane (*J.*, 1951, 3028) was not isolated, probably because the 2 : 4 : 6-trihydroxy-3-methyl-*n*-butyrophenone residue is, as Boehm (*loc. cit.*) observed, much less resistant to fission in alkaline media than butanofilicinic acid. From our studies on the nature of the polyhydroxydiphenylmethane disproportionation reaction (*J.*, 1951, 2021) it appeared clear to us that the production of *CCC*-trimethylphloroglucinol from a compound having structure (II) depended on the mechanism already proposed by Birch (*J.*, 1951, 3028) † and hence that in all probability flavaspidic acid was represented by (II).

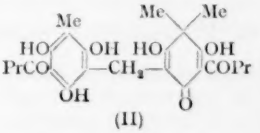
The synthesis of flavaspidic acid from butanofilicinic acid (V; R = Pr·CO) and 2 : 4 : 6-trihydroxy-3-methyl-*n*-butyrophenone (IV) by the method employed for 5 : 5′-di-*n*-

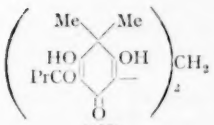
* Part II, *J.*, 1933, 1617.

† The work summarised in this paper and in the earlier memoir (*J.*, 1951, 2021), together with the derivation of structure (II) for flavaspidic acid, were described in a thesis presented in July, 1950, by Dr. T. H. Simpson for the degree of Ph.D. of this University. A.R.

butyryl-2 : 4 : 6 : 2′ : 4′ : 6′-hexahydroxy-3 : 3′-dimethyldiphenylmethane (*loc. cit.*) now confirms the structure (II). Although the intermediate butanofilicinic acid has not yet


(I)


(II)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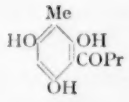
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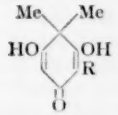

(V)

been synthesised the structure of this compound has been substantiated by its hydrolysis (Boehm, *loc. cit.*) to *n*-butyric acid and filicinic acid (V; R = H), the synthesis of which was described in Part II (*J.*, 1933, 1617).

Experimental

Flavaspidic Acid.—(*a*) The tedious method for the isolation of flavaspidic acid described by Boehm (*Arch. exp. Path. Pharm.*, 1897, **38**, 33) was found unsuitable for large-scale work and the following was adopted. A solution of male-fern extract (1250 g.) in acetone (750 ml). was added dropwise in 3 hr. to well-stirred water (10 l.) containing magnesium oxide (3 kg.), and the mixture agitated for 10 hr. Acidification of the filtered aqueous liquor and the washings from the magnesium salts (10 l. × 3) with dilute hydrochloric acid gave a yellow granular precipitate which was powdered and dried in a vacuum (P_2O_5) (yield, 88 g.). On slow evaporation (14 days) a solution of this solid (20 g.) in ether deposited flavaspidic acid which, on recrystallisation from methanol, formed bright yellow prisms, m. p. 157—158°, with a deep red ferric reaction in alcohol; occasionally the form of m. p. 92° was obtained (Found: C, 64·5, 64·5; H, 7·0, 6·8. Calc. for $C_{24}H_{30}O_8$: C, 64·5; H, 7·0%. Calc. for $C_{24}H_{28}O_8$: C, 64·8; H, 6·4%). Butanofilicinic acid was prepared from flavaspidic acid by Boehm's method (*loc. cit.*) and had m. p. 95° and a red-brown ferric reaction in alcohol (Found: C, 64·1; H, 7·4. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%). With diazoaminobenzene it gave the monoazo-derivative, forming orange yellow prisms, m. p. 137°, from methanol (Boehm, *loc. cit.*).

With warm alcoholic diazoaminobenzene flavaspidic acid gave the azo-derivative of 2 : 4 : 6-trihydroxy-3-methyl-*n*-butyrophenone, m. p. 181—182°, identical with a specimen from the synthetic ketone (Part I, *J.*, 1933, 819) (cf. Boehm, *loc. cit.*) (Found: C, 65·2; H, 5·8; N, 8·8. Calc. for $C_{17}H_{18}O_4N_2$: C, 65·0; H, 5·8; N, 8·9%). Attempts to isolate the azo-derivative of butanofilicinic acid from the reaction mixture were unsuccessful.

A solution of flavaspidic acid (2 g.) in 2N-sodium carbonate (30 ml.) was heated on the steam-bath for ½ hour, cooled, and acidified with dilute hydrochloric acid. Trituration of the flocculent product with methanol (10 ml. × 2) left a colourless residue (0·12 g.), m. p. 138—140°, of albaspidin which on crystallisation from methanol had m. p. 148°, identical with a specimen prepared by the interaction of butanofilicinic acid (0·43 g.), 40% aqueous formaldehyde, and sulphuric acid (1 ml.) in alcohol (10 ml.) at room temperature.

(*b*) A mixture of 2 : 4 : 6-trihydroxy-3-methyl-*n*-butyrophenone (0·5 g.), butanofilicinic acid (2 g.), paraformaldehyde (2 g.), methanol (15 ml.), and sulphuric acid (1 ml.) was agitated at room temperature for 3 days. After the addition of water, the solid was collected, washed, and extracted with hot methanol, leaving slightly impure albaspidin. On being diluted with water (2 ml.) the methanolic extract slowly deposited flavaspidic acid (0·2 g.), m. p. 157—158°, after purification from a little methanol, the properties and reactions of which were identical with those of the natural compound (Found: C, 64·7; H, 6·8%).

University of Liverpool. [*Received, March 5th*, 1953.]

377. *The Chemistry of Fungi. Part XVII.* Dehydroeburicoic Acid.*

By R. M. Gascoigne, Alexander Robertson, and J. J. H. Simes.

Eburicoic acid is considered to have the empirical formula $C_{31}H_{50}O_3$.

The unsaturated acid with a conjugated diene system (Part XVI *) present in the mixed metabolic product of *Lentinus dactyloides* Clel. has been shown to be dehydroeburicoic acid by the oxidation of the mixture and isolation of dehydroeburiconic acid, identical with a specimen prepared from eburicoic acid by standard procedure. The epimer of dehydroeburicoic acid has also been prepared.

Experiments on the oxidation of the ring system of *O*-acetyleburicoic acid and a number of its derivatives are described. The similarities of eburicoic and dehydroeburicoic acid to lanosterol and agnosterol respectively are discussed.

From the results of the analysis of eburicoic acid and numerous derivatives (present work and unpublished observations) the compound is now considered to have the formula $C_{31}H_{50}O_3$, and not $C_{30}H_{48}O_3$ suggested earlier (*Nature*, 1951, **167**, 652; cf. Lahey and Strasser, *J.*, 1951, 873). This is supported by the molecular weight of methyl *O*-acetyldihydroeburicoate which was determined for us, through the kindness of Professor F. E. King of Nottingham, by Dr. S. C. Wallwork, using the *X*-ray method (Found : *M*, 526. Calc. for $C_{34}H_{56}O_4$: *M*, 529).

During the isolation of eburicoic acid from five species of fungi belonging to the class Basidiomycetes grown on a synthetical medium (Part XVI *) it was observed that in two species, *Lentinus dactyloides* Clel. and *Fomes officinalis* Fr., the acid was accompanied by a conjugated compound, having an absorption maximum at 243 mμ with subsidiary peaks at 236 and 251 mμ. The resolution of the mixtures proved difficult and, although small amounts of eburicoic acid could be separated by chromatography, the conjugated compound was not isolated. Other methods of separation have been explored, including crystallisation of various amine salts of the mixed acids from a variety of solvents, a technique which was successful with diterpene acids (Harris *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 334, 2079, **3671**, **3674**) but in the present instance gave only a partial separation. The conjugated compound did not react with maleic anhydride even under the conditions in which the conjugated system of abietic acid ($\lambda_{max.}$ 241 mμ) is isomerised to form the adduct of lævopimaric acid (Bacon and Ruzicka, *Chem. and Ind.*, 1936, **55**, 546). Thus the acidic complexes appeared to resemble the mixture of lanosterol and dihydrolanosterol, and of agnosterol and dihydroagnosterol, which could be resolved only by oxidation with chromic anhydride to a mixture of ketones, separable by fractional crystallisation (Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759; 1946, **29**, 204). Consequently an oxidation procedure was applied to the product from *Lentinus dactyloides* and by the Oppenauer method this gave a mixture of keto-acids from which a spectroscopically pure compound [$\lambda_{max.}$ 243 mμ (log ε 4·24)] was isolated as the less soluble component by a lengthy fractional crystallisation. The similarity of the ultra-violet absorption of this compound to that of agnosterol, together with other considerations enumerated below, suggested that the conjugated compound co-existent with eburicoic acid in the fungi might be a dehydroeburicoic (eburicotrienolic, Part XVI) acid and consequently methods of preparation of a compound of this type from eburicoic acid were investigated. For this purpose three principal methods appeared feasible, *viz.*, dehydrogenation by selenium dioxide or *N*-bromosuccinimide, and oxidation by chromic acid to an αβ-unsaturated ketone capable of being reduced to an allyl alcohol which would be readily dehydrated to give the conjugated system. Whereas selenium dioxide reacted readily with *O*-acetyldihydroeburicoic acid, giving *O*-acetyldehydrodihydroeburicoic acid ($\lambda_{max.}$ 243 mμ, log ε 4·25) in good yield, *O*-acetyleburicoic acid, under similar conditions, formed intractable

* Part XVI, *J.*, 1951, 2346.

products owing to simultaneous attack at the reactive double bond. Similarly, with *N*-bromosuccinimide under a variety of conditions *O*-acetyleburicoic acid formed complex mixtures. More success was achieved with the third method. Oxidation of *O*-acetyleburicoic acid with chromic anhydride under relatively mild conditions led to the introduction of carbonyl groups with the formation of only small amounts of by-products. On deacetylation the main reaction product was found to be a difficultly separable mixture of colourless ketoeburicoic acid ($\lambda_{max.}$ 253 mμ, log ε 3·97), and yellow diketoeburicoic acid ($\lambda_{max.}$ 270 mμ, log ε 3·90). As the required monoketo-acid appeared to be readily oxidised to the diketo-compound the maximum yield of the required ketoeburicoic acid was obtained with conditions where some eburicoic acid was recovered unchanged. Reduction of the monoketo-acid with sodium in boiling amyl alcohol led directly to dehydroeburicoic acid and the intermediate hydroxyeburicoic acid was not isolated. Thus obtained, dehydroeburicoic acid had $\lambda_{max.}$ 243 mμ (log ε 4·24) and on oxidation by the Oppenauer method yielded dehydroeburiconic acid which, by comparison of their methyl esters, infra-red absorption spectra, and other physical properties, was found to be identical with the keto-acid separated from the product formed by the Oppenauer oxidation of the mixed acids isolated from *Lentinus dactyloides*. The conjugated hydroxy-acid produced by this mould along with eburicoic acid is, therefore, either dehydroeburicoic acid or its epimer. The latter possibility has been excluded by a comparison with the corresponding *epi*-compounds which can be separated readily from their respective isomerides and, therefore, since one component of the mixed acetylated acids from *Lentinus dactyloides* Clel. is *O*-acetyleburicoic acid (Part XVI) the other is clearly *O*-acetyldehydroeburicoic acid.

The production of eburicoic and dehydroeburicoic acid by fungi is analogous to the occurrence of agnosterol and lanosterol in wool wax. The wool-wax mixture also contains dihydrolanosterol and dihydroagnosterol (Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472) but no evidence has been obtained indicating the presence of dihydro-compounds in the fungal mixtures. The comparisons enumerated below show that eburicoic and dehydroeburicoic acids are very similar in many respects to lanosterol and agnosterol respectively, and provide circumstantial evidence that the structural residues (I) and (II) of the last-named compounds are present in eburicoic and dehydroeburicoic acid respectively.

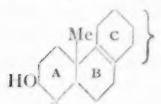
(1) *O*-Acetyldihydroeburicoic acid does not exhibit infra-red absorption in the 12-μ region that could be attributed to a carbon–carbon double bond, thus indicating that the double bond present in the molecule is tetrasubstituted. The ultra-violet absorption spectra of dehydroeburicoic acid and agnosterol are very similar whilst the infra-red absorption of *O*-acetyldehydrodihydroeburicoic acid exhibits a peak at 813 cm.$^{-1}$, and Voser, Montavon, Günthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893) record that dihydroagnosterol acetate has strong absorption in the infra-red at 814 cm.$^{-1}$ which they ascribe to the trisubstituted double bonds.

(2) Reduction of *O*-acetyldehydroeburicoic acid with Adams' catalyst at room temperature and atmospheric pressure or at 30 atmospheres produced *O*-acetyldehydrodihydroeburicoic acid ($\lambda_{max.}$ 243 mμ, log ε 4·26), identical with the product formed by selenium dioxide oxidation of *O*-acetyldihydroeburicoic acid, in which only the exocyclic double bond has been reduced. Similarly, Birchenough and McGhie (*J.*, 1949, 2038) record that the two nuclear double bonds of dihydroagnosterol cannot be hydrogenated (cf. also Ruzicka *et al.*, *loc. cit.*, 1946).

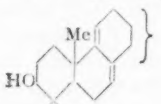
(3) The formation of keto- and diketo-eburicoic acid by the chromic anhydride oxidation of *O*-acetyleburicoic acid is in accordance with the properties of tetracyclic triterpenes in general (cf. Haines and Warren, *J.*, 1950, 1562). For the mono- and di-keto-compounds thus formed from dihydrolanosterol the partial formulæ (III) and (IV) have been established (Voser *et al.*, *loc. cit.*; see also Barton, Fawcett, and Thomas, *J.*, 1951, 3147).

The oxidation of *O*-acetyldehydrodihydroeburicoic acid and *O*-acetyldihydroeburicoic acid with chromic anhydride yielded *O*-acetyldihydrodiketoeburicoic acid, the methyl ester of which has been described by Lahey and Strasser (*J.*, *loc. cit.*). Similarly, oxidation of dihydroagnosteryl acetate and of dihydrolanosteryl acetate, respectively, yielded the

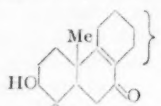
same dihydrodiketolanosteryl acetate (Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Reduction of methyl *O*-acetyldihydrodiketoeburicoate with zinc and acetic acid yielded colourless methyl acetyltetrahydrodiketoeburicoate ($\lambda_{max.}$ 295 mμ, log ε 1·80), where the ene-1 : 4-dione chromophore has been reduced to a 1 : 4-diketonic system as in the conversion of dihydrodiketolanosteryl acetate into diketolanostanyl acetate (Dorée *et al.*, *loc. cit.*) having a structure of type (V) (Voser *et al.*, *loc. cit.*).



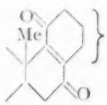
(I)



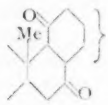
(II)



(III)



(IV)



(V)

The ultra-violet absorption spectra of keto- and diketo-eburicoic acid are similar to those of dihydroketolanosterol and dihydrodiketolanosterol respectively, and *O*-acetyldihydrodiketoeburicoic acid does not show absorption in the 12-μ region which could be attributed to a carbon–carbon double bond. Dihydrodiketolanosteryl acetate does not show ethylenic absorption in the infra-red and from this Voser *et al.* (*loc. cit.*) deduced that the ene-1 : 4-dione system must have the transoid arrangement shown in (IV) since normally double bonds conjugated with keto-groups have strong infra-red absorption. These considerations suggest that the structures (III), (IV), and (V) are applicable also to keto-, diketo-, and tetrahydrodiketo-eburicoic acid respectively.

(4) The methods which have been used to convert eburicoic and dihydroeburicoic acid into their respective dehydro-compounds are those used in the conversion of dihydrolanosterol into dihydroagnosterol, *viz.*, (*a*) reduction and dehydration of ketoeburicoic acid (cf. the reduction and dehydration of dihydroketolanosterol; Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Cavalla and McGhie, *J.*, 1951, **744**) and (*b*) the action of selenium dioxide on *O*-acetyldihydroeburicoic acid (cf. Bellamy and Dorée, *J.*, 1941, **176**; Dorée, McGhie, and Kurzer, *J.*, 1949, 570); the action of *N*-bromosuccinimide on *O*-acetyleburicoic acid gave an inseparable mixture. Further, Lahey and Strasser (*loc. cit.*) observed that with perbenzoic acid methyl *O*-acetyldihydroeburicoate gave a compound having $\lambda_{max.}$ 243 mμ (log ε 4·24), which they term methyl acetyl*iso*-eburicoate, and which is undoubtedly identical with methyl *O*-acetyldehydrodihydroeburicoate now obtained. As Lahey and Strasser indicated, the formation of this ester is analogous to the conversion of dihydrolanosteryl into dihydroagnosteryl acetate by perbenzoic acid (Birchenough and McGhie, *loc. cit.*).

In their comparatively ready conversion into dehydro-derivatives lanosterol and eburicoic acid can be differentiated from other tetracyclic triterpenes, *viz.*, euphol, tirucallol, euphorbol, and elemadienolic acid. Thus dihydrolanosteryl acetate and *O*-acetyldihydroeburicoic acid react readily with selenium dioxide in hot acetic acid to yield their respective dehydro-compounds under conditions where dihydroeuphyl acetate (Vilkas, Dupont, and Dulou, *Bull. Soc. chim.*, 1949, 813) and elemenolic acid (Ruzicka, Rey, and Spillmann, *Helv. Chim. Acta*, 1942, **25**, 1375) are not attacked. Similarly, the epoxides of dihydrolanosteryl acetate (Birchenough and McGhie, *loc. cit.*) and *O*-acetyldihydroeburicoic acid (Lahey and Strasser, *loc. cit.*) formed by perbenzoic acid are very unstable, yielding the dehydro-compounds virtually spontaneously, whereas the epoxides from dihydroeuphyl, dihydrotirucallyl, and dihydroeuphorbyl acetate require treatment with a dehydrating agent to convert them into the dehydro-compounds (Barbour, Bennett, and Warren, *J.*, 1951, 2540).

(5) The molecular-rotation differences observed on acetylation and oxidation of the tetracyclic triterpenes (Table 1; cf. Heilbron, Jones, and Robins, *J.*, 1949, 444) show considerable divergencies between most of the members of this group. These divergencies are in contrast to the uniformity of the values in the case of eburicoic acid and its derivatives compared with those of lanosterol and its corresponding derivatives. This similarity between eburicoic acid and lanosterol appears also in the molecular-rotation differences observed with the dehydro-compounds (Table 2) and with the ene-1 : 4-diones prepared from members of the tetracyclic group (Table 3).

TABLE 1.

	$[M]_D$					
	Acetate	Ketone	ΔAc	ΔKet	Refs. to values of $[\alpha]_D$ †
Eburicoic acid	+235°	+249°	+248°	+ 14°	+ 13°	1
Dihydroeburicoic acid	+215	+253	—	+ 36	—	1
Methyl eburicoate	+222	+256	+287	+ 34	+ 65	1
Methyl dihydroeburicoate	+219	+270	—	+ 51	—	1
Lanosterol	+258	+313	+333	+ 55	+ 75	2, 3
Dihydrolanosterol	+250	+278	+318	+ 28	+ 68	2, 3, 4, 5, 6
Euphol	+134	+202	+306	+ 68	+172	7, 8, 9, 10, 32
Dihydroeuphol	+131	+165	+277	+ 34	+146	7, 8, 9
*epi*Elemadienolic acid	+ 43	+130	+205	+ 87	+162	11, 12, 13, 14
*epi*Elemenolic acid	+ 69	+ 80	+197	+ 11	+128	11, 12, 13
Elemadienolic acid	−110	−200	+205	− 90	+315	11, 12, 13, 14, 15, 16
Elemenolic acid	− 83	−160	+197	− 77	+280	11, 12, 13, 14, 17, 18, 19
Methyl elemadienolate	− 68	−216	+162	−148	+230	11, 12, 14
Methyl elemenolate	− 28	−185	—	−157	—	11, 12, 14, 19
Tirucallol	(+19) *	(−77) *	—	(− 96)	—	20
Dihydrotirucallol	(+13) *	(−55) *	+171	(− 68)	(+158)	20, 21
Euphorbol	0	0	+ 93	0	+ 93	7, 22
Butyrospermol	− 53	+ 52	−162	+105	−109	23, 24
Dihydrobutyrospermol	− 56	+ 52	−188	+108	−132	23, 24

* Measurement of $[\alpha]_D$ in benzene solution. † See Table 3.

TABLE 2.

	$[M]_D$				Refs. to values
	Acetate	Ketone	ΔAc	ΔKet	of $[\alpha]_D$ *
Dehydroeburicoic acid	+188°	+317°	+131°	+129°	−59°	1
Dehydrodihydroeburicoic acid	+184	+346	+113	+162	−71	1
Methyl dehydroeburicoate	+207	+357	+139	+150	−68	1
Methyl dehydrodihydroeburicoate	+204	+364	+116	+160	−88	1
Agnosterol	+283	+414	+212	+131	−71	25
Dihydroagnosterol	+284	+411	+202	+127	−82	4, 5, 25, 26
Dehydrodihydroeuphol (Dehydroeuphenol)	−508	− 42	—	+466	—	27
Dehydrodihydrotirucallol (Dehydrotirucallenol)	−701	−639	—	+ 62	—	27
Dehydrodihydroeuphorbol (Dehydroeuphorbenol)	−581	−652	—	− 71	—	27

* See Table 3.

TABLE 3.

	$[M]_D$				Refs. to values
Ene-1 : 4-dione prepared from	Acetate	Ketone	ΔAc	ΔKet	of $[\alpha]_D$
Eburicoic acid	+314°	+395°	—	+81°	—	1
Dihydroeburicoic acid	+301	+391	+664°	+90	+363°	1
Methyl dihydroeburicoate	+306	+395	+595	+89	+289	1
Dihydrolanosterol	+356	+454	+787	+98	+431	4, 28, 29, 30
Elemenolic acid	− 54	−148	+ 37	−94	+ 91	12, 31
Dihydroeuphol	+128	+114	+141	−14	+ 13	21, 32
Dihydrotirucallol	−112	− 85	—	+27	—	21
Dihydroeuphorbol	−270	−200	—	+70	—	22

[1] For eburicoic acid and its derivatives see Lahey and Strasser (*loc. cit.*), Part XVI (*loc. cit.*), and this communication. [2] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759. [3] Wieland, Pasedach, and Ballauf, *Annalen*, 1937, **529**, 68. [4] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. [5] Windaus and Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51. [6] Wieland and Benend, *ibid.*, 1942, **274**, 215. [7] Newbold and Spring, *J.*, 1944, 249. [8] Jeger and Krusi, *Helv. Chim. Acta*, 1947, **30**, 2045. [9] Roth and Jeger, *ibid.*, 1949, **32**, 1620. [10] Bennett and Warren, *J.*, 1950, 697. [11] Ruzicka and Hausermann, *Helv. Chim. Acta*, 1942, **25**, 439. [12] Ruzicka, Rey, Spillmann, and Baumgartner, *ibid.*, 1943, **26**, 1638. [13] Bilham and Kon, *J.*, 1942, 544. [14] Ruzicka, Rey, and Spillmann, *Helv. Chim. Acta*, 1942, **25**, 1375. [15] Lieb and Mladenovic, *Monatsh.*, 1932, **61**, 274. [16] *Idem*, *ibid.*, 1931, **58**, 59. [17] Ruzicka and Furter, *Helv. Chim. Acta*, 1932, **15**, 472. [18] Lieb and Mladenovic, *Monatsh.*, 1932, **59**, 228. [19] Ruzicka, Wakeman, Furter, and Goldberg, *Helv. Chim. Acta*, 1932, **15**, 1454. [20] Haines and Warren, *J.*, 1949, 2554. [21] *Idem*, *J.*, 1950, 1562. [22] Barbour, Warren, and Wood, *J.*, 1951, 2537. [23] Heilbron, Jones, and Robins, *J.*, 1949, 444. [24] Seitz and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1626. [25] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204. [26] Birchenough and McGhie, *J.*, 1949, 2038. [27] Barbour, Bennett, and Warren, *J.*, 1951, 2540. [28] Birchenough and McGhie, *J.*, 1950, 1249. [29] Cavalla and McGhie, *J.*, 1951, 744. [30] Cavalla and McGhie, *J.*, 1951, 834. [31] Ruzicka, Rey, Spillmann, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1659. [32] Christen, Dünnenberger, Roth, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1756.

Experimental

Specific rotations were measured in chloroform, 1-dm. tubes being used except where otherwise stated. Ultra-violet absorption spectra were determined in alcohol with a Unicam spectrophotometer.

Infra-red absorption measurements were made with a Grubb Parsons single-beam spectrometer; 5—8% solutions of carbon disulphide and a 0·2-mm. cell were employed except where stated.

Isolation of Dehydroeburiconic Acid from Mixed Acids of Lentinus dactyloides *Clel.*—Aluminium *tert.*-butoxide (6·9 g.) was added to a solution of the mixed eburicoic and dehydroeburicoic acid (3·3 g.; $\lambda_{max.}$ 243 mμ, $E^{1\%}_{1\,cm.}$ 100) from the mycelium of *Lentinus dactyloides* Clel. in dioxan (28 ml.) containing *cyclo*hexanone (8 ml.), and the mixture, which became clear when warmed, was heated under reflux for 12 hr., cooled, and treated with an excess of dilute sulphuric acid. After the removal of the solvents in a current of steam the residual solid was isolated, washed with water, dried, and crystallised from alcohol (charcoal). The first fraction (1·13 g.) had m. p. 220—225°, $\lambda_{max.}$ 243 mμ, $E^{1\%}_{1\,cm.}$ 179, and the second (1·52 g.) had m. p. 218—225°, $\lambda_{max.}$ 243 mμ, $E^{1\%}_{1\,cm.}$ 90. Thus obtained, the two products were subjected to a prolonged fractional crystallisation from alcohol in which fractions having equal intensities of absorption at 243 mμ were combined. *Dehydroeburiconic acid* was ultimately obtained and, on repeated recrystallisation from alcohol, had a constant value for the absorption at points of maximum intensity; the yield was 130 mg. (no attempt was made to isolate eburiconic acid, named eburicodienonic acid in Part XVI, *loc. cit.*). This acid formed colourless needles, m. p. 241—242° (from alcohol), $\lambda_{max.}$ 234, 243, 252 mμ (log ε 4·19, 4·25, 4·08) and an inflexion at about 285 mμ (log ε 1·78), $[\alpha]_D^{20}$ +27·0° (*c*, 1·9, 0·5-dm. micro-tube) (Found: C, 79·8; H, 10·1. $C_{31}H_{46}O_3$ requires C, 79·8; H, 9·9%). Determined with a paste in "Nujol" the infra-red absorption spectra of this compound was identical with that of a specimen prepared from eburicoic acid. The *methyl* ester was prepared with ethereal diazomethane containing a trace of methanol and on purification from methanol formed needles, m. p. 159—160°, $[\alpha]_D^{16}$ +28·5° (*c*, 2·53 in 0·5-dm. micro-tube) (Found: C, 80·1; H, 10·3. $C_{32}H_{48}O_3$ requires C, 80·0; H, 10·1%).

Oxidation of O-*Acetyleburicoic Acid with Chromic Acid.*—A solution of *O*-acetyleburicoic acid (17 g.) in acetic acid (750 ml.) was treated with chromic anhydride (5·55 g.) dissolved in acetic acid (200 ml.) containing water (40 ml.), kept for 4 days, and diluted with water (10·0 l.). The resulting precipitate was boiled with 10% alcoholic potassium hydroxide (300 ml.) for 1 hr. and, after dilution with water (750 ml.), the hydrolysate was concentrated until the potassium salts began to separate. On isolation the resulting mixed salts were digested with boiling 0·1N-sodium hydroxide (2 l.), leaving the potassium salt of unchanged eburicoic acid (2·5 g.). Acidification of the cooled extract gave a mixture of keto- and diketo-eburicoic acid; more of this mixture (1·0 g.) was obtained by acidification of the concentrated liquor from the crude salts and boiling the product with 15% aqueous sodium carbonate, whereby a mixture of the insoluble sodium salts of the acids was obtained which was washed with aqueous sodium carbonate and decomposed with 2N-hydrochloric acid. Crystallised from aqueous alcohol, the mixed keto-acids formed light yellow slender needles (9·8 g.), m. p. 251—254°, $\lambda_{max.}$ 254—255 mμ. This product (2·7 g.) was acetylated with pyridine and acetic anhydride on the steam-bath, and a solution of the mixed acetates in benzene (200 ml.) was poured on a column of neutralised aluminium oxide (130 g.) which was then washed with benzene (1·2 l.) to remove mixed anhydro-compounds (0·61 g.), presumably formed during acetylation of the keto-acids. Elution with acetone–benzene (1 l.; 1 : 19) then gave O-*acetylketoeburicoic acid* (0·92 g.), $\lambda_{max.}$ 253 mμ, which formed colourless needles, m. p. 229—231°, $[\alpha]_D^{20}$ +18° (*c*, 2·5; 0·5-dm. micro-tube) (Found: C, 75·6; H, 9·4. $C_{33}H_{50}O_5$ requires C, 75·2; H, 9·6%), and on deacetylation yielded *ketoeburicoic acid*, separating from dilute alcohol in colourless needles, m. p. 253—254°, $[\alpha]_D^{21}$ +24° (*c*, 1·63; 0·5-dm. micro-tube), $\lambda_{max.}$ 253 mμ (log ε 3·97) with an inflexion at about 332 mμ (log ε 1·71) (Found, in specimen sublimed in a high vacuum: C, 76·7; H, 9·9. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%). After the elution of *O*-acetylketoeburicoic acid the column was washed with acetone–benzene (1 : 10, then 1 : 5) and gave a series of fractions the $\lambda_{max.}$ of which progressively increased. Finally, elution with acetone (1·3 l.) furnished O-*acetyldiketoeburicoic acid* (0·29 g.), which formed pale yellow needles, m. p. 279—280°, $[\alpha]_D^{21}$ +73° (*c*, 4·75; 0·5-dm. micro-tube), from dilute alcohol (Found: C, 73·4; H, 8·7. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·9%). On deacetylation this acetate gave *diketoeburicoic acid* which separated from dilute alcohol in pale yellow needles, m. p. 260—262°, $[\alpha]_D^{21}$ +63° (*c*, 1·1), $\lambda_{max.}$ 270, 337 mμ (log ε 3·90, 1·68) with an inflexion at about 405 mμ (log ε 1·40) (Found, in specimen sublimed in a high vacuum: C, 74·7; H, 9·2. $C_{31}H_{46}O_5$ requires C, 74·7; H, 9·3%).

Dehydroeburicoic Acid.—To a boiling solution (oil-bath) of ketoeburicoic acid (0·09 g.) in *n*-amyl alcohol sodium (1 g.) was added gradually during 1 hr., with more *n*-amyl alcohol to maintain a clear solution. The cooled mixture was treated with water followed by an excess of dilute hydrochloric acid, the amyl alcohol layer was isolated, and the alcohol removed with steam, leaving a pale yellow solid (0·08 g.), m. p. 255—265°, $\lambda_{max.}$ 234, 243, 252 mμ, $E^{1\%}_{1\,cm.}$ 202, 236, 161, which on being recrystallised five times from ethyl acetate gave *dehydroeburicoic acid* in slender needles, m. p. 286—288°, $[\alpha]_D^{23}$ +40° (*c*, 0·2; *l*, 4·0), $\lambda_{max.}$ 234, 243, 252 mμ, $E^{1\%}_{1\,cm.}$ 320, 375, 252 (Found: C, 79·1; H, 10·4. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). *Methyl dehydroeburicoate* was prepared from the acid with ethereal diazomethane containing methanol, and on crystallisation from benzene–light petroleum and then aqueous methanol formed colourless needles, m. p. 146·5—147·5°, $[\alpha]_D^{23}$ +43° (*c*, 3·1; 0·5-dm. micro-tube) (Found: C, 79·6; H, 10·5. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). By the pyridine–acetic anhydride method the acid gave O-*acetyldehydroeburicoic acid* which separated from alcohol in needles, m. p. 255—256°, $[\alpha]_D^{21}$ +62° (*c*, 2·4) (Found: C, 77·7; H, 10·0. $C_{33}H_{50}O_4$ requires C, 77·6; H, 9·9%). On admixture with *O*-acetyleburicoic acid it gave no depression in the m. p. Formed by means of ethereal diazomethane containing a trace of methanol, *methyl* O-*acetyldehydroeburicoate* formed needles, m. p. 159—160°, $[\alpha]_D^{23}$ +68° (*c*, 4·7; 0·5-dm. tube) from methanol (Found: C, 77·7; H, 10·1. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%).

Dehydroeburiconic Acid from Dehydroeburicoic Acid.—A mixture of dehydroeburicoic acid (0·5 g.), aluminium *tert.*-butoxide (1 g.), dioxan (4·25 ml.), and *cyclo*hexanone (1·15 ml.) was heated under reflux for 8 hr. and the resulting dehydroeburiconic acid was isolated in the usual manner by the method employed in the isolation of the compound from metabolic acids. Recrystallised from methanol, the acid formed needles (0·3 g.), m. p. 240—242°, $[\alpha]_D^{21}$ +28° (*c*, 0·8), $\lambda_{max.}$ 234, 243, 252 mμ (log ε 4·19, 4·26, 4·08) with an inflexion at about 285 mμ (log ε 1·79) (Found: C, 79·5; H, 10·1. Calc. for $C_{31}H_{46}O_3$: C, 79·8; H, 9·9%). Methyl dehydroeburiconate separated from methanol in needles, m. p. 159—160°, $[\alpha]_D^{21}$ +29·5° (*c*, 2·5; 0·5-dm. micro-tube) (Found: C, 80·0; H, 10·2. Calc. for $C_{32}H_{48}O_3$: C, 80·0; H, 10·1%).

Dehydrodihydroeburicoic Acid.—A solution of *O*-acetyldihydroeburicoic acid (2·7 g.), in 95% acetic acid (75 ml.), containing selenium dioxide (3·6 g.), was refluxed for 3 hr., filtered, and diluted with water. After having been crystallised from dilute alcohol, the product was chromatographed in benzene on a short column of neutralised aluminium oxide. The resulting O-*acetyldehydrodihydroeburicoic acid* (2·1 g.) separated from alcohol in colourless needles, m. p. 270—273°, $[\alpha]_D^{21}$ +65° (*c*, 2·5), $\lambda_{max.}$ 234, 243, 252 mμ (log ε 4·18, 4·25, 4·06) (Found: C, 77·0; H, 10·1. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·2%). The same compound (0·18 g.) was obtained by hydrogenation of *O*-acetyldehydroeburicoic acid (0·2 g.), dissolved in alcohol (25 ml.), with a platinum catalyst and hydrogen (1·05 mol. absorbed) at room temperature and pressure or at a pressure of 30 atm. Methyl *O*-acetyldehydrodihydroeburicoate formed needles, m. p. 164—164·5°, $[\alpha]_D^{20}$ +69° (*c*, 2·0), from methanol (Found: C, 77·1; H, 10·3. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·3%) (cf. Lahey and Strasser, *loc. cit.*).

O-Acetyldehydrodihydroeburicoic acid (0·8 g.) was deacetylated with boiling 10% alcholic potassium hydroxide (50 ml.) during 3 hr. and the hydrolysate treated with water (25 ml.). On evaporation of the greater part of the alcohol potassium dehydrodihydroeburicoate separated which on decomposition in alcohol with hydrochloric acid gave the *acid*, separating from alcohol in slender needles, (0·65 g.), m. p. 298—300°, $[\alpha]_D^{20}$ +39° (*c*, 0·16; 4-dm. tube) (Found: C, 78·7; H, 10·8. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). Formed by deacetylation of methyl *O*-acetyldehydrodihydroeburicoate the *methyl* ester formed needles, m. p. 162—163°, with softening at 148°, $[\alpha]_D^{20}$ +42° (*c*, 4·4; 0·5-dm. micro-tube), from methanol (Found: C, 79·3; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Dehydrodihydroeburiconic Acid.—Oxidation of dehydrodihydroeburicoic acid (0·5 g.) with aluminium *tert.*-butoxide (1 g.) and *cyclo*hexanone (1·15 ml.) in boiling dioxan (4·25 ml.) for 8 hr. gave *dehydrodihydroeburiconic acid* which separated from alcohol in needles, (0·3 g.), m. p. 252—254°, $[\alpha]_D^{21}$ +24° (*c*, 1·7) (Found: C, 79·5; H, 10·5. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%). The *methyl* ester crystallised from methanol as needles, m. p. 155—155·5°, $[\alpha]_D^{23}$ +24° (*c*, 0·9) (Found: C, 79·6; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%).

Dihydrodiketoeburicoic Acid.—(*a*) Oxidation of *O*-acetyldihydroeburicoic acid (0·5 g.) in acetic acid (20 ml.) was effected with chromic anhydride (0·33 g.) in acetic acid (6 ml.) and water (1·2 ml.) at room temperature during 7 days, or at 80° for 1 hr. The solid obtained by dilution of the reaction mixture with water (450 ml.) was deacetylated with hot 10% alcoholic potassium hydroxide (50 ml.), and the resulting almost pure dihydrodiketoeburicoic acid isolated by way of the potassium salt and recrystallised from dilute alcohol having m. p. 274—276° (yield,

0·35 g.). This product was acetylated and the resulting *O-acetyldihydrodiketoeburicoic acid* purified by chromatography from benzene on neutralised aluminium oxide, and then crystallised from dilute alcohol, forming needles (0·25 g.), m. p. 286—288° (decomp.), $[\alpha]_D^{21}$ +72° (*c*, 2·1), $\lambda_{max.}$ 269, 332—334 mμ (log ε 3·97, 1·87) with an inflexion at about 405 mμ (log ε 1·6) (Found: C, 72·9; H, 9·5. $C_{33}H_{50}O_6$ requires C, 73·0; H, 9·3%). The methyl ester separated from methanol in thick yellow prisms, m. p. 172°, $[\alpha]_D^{22}$ +71° (*c*, 0·6), $\lambda_{max.}$ 269—270, 332—334 mμ (log ε 3·99, 1·89) with an inflexion at about 405 mμ (log ε 1·65) (Found: C, 73·6; H, 9·6. Calc. for $C_{34}H_{52}O_6$: C, 73·3; H, 9·4%) (cf. Lahey and Strasser, *loc. cit.*).

Deacetylation of *O*-acetyldihydrodiketoeburicoic acid gave *dihydrodiketoeburicoic acid* which crystallised from dilute alcohol in slender needles, m. p. 276—277°, $[\alpha]_D^{18}$ +60° (*c*, 0·6) (Found, in specimen sublimed in a high vacuum: C, 74·6; H, 9·7. $C_{31}H_{48}O_5$ requires C, 74·4; H, 9·7%). The *methyl* ester separated from methanol in yellow needles, m. p. 88°, containing solvent of crystallisation. Recrystallised from light petroleum (b. p. 60—80°), the compound formed yellow needles, m. p. 140—141°, $[\alpha]_D^{21}$ +59·5° (*c*, 1·42) (Found: C, 75·1; H, 10·0. $C_{32}H_{50}O_5$ requires C, 74·7; H, 9·8%).

(*b*) The oxidation of *O*-acetyldehydrodihydroeburicoic acid by method (*a*) gave a product from which *O*-acetyldihydrodiketoeburicoic acid was isolated by chromatography from benzene on neutralised aluminium oxide and on recrystallisation had m. p. and mixed m. p. 286—288° (decomp.), $[\alpha]_D^{21}$ +70° (*c*, 1·2), and the expected ultra-violet absorption spectrum (Found: C, 73·3; H, 9·4%). The methyl ester had m. p. and mixed m. p. 171·5—172°, $[\alpha]_D^{21}$ +69° (*c*, 1·2) (Found: C, 73·6; H, 9·6%). The ultra-violet and infra-red absorption spectra of the specimens of methyl *O*-acetyldihydrodiketoeburicoate prepared by methods (*a*) and (*b*) were identical.

Methyl O-Acetyltetrahydrodiketoeburicoate.—Zinc dust (1 g.) was added gradually to a boiling solution (yellow) of methyl *O*-acetyldihydrodiketoeburicoate (0·18 g.) in acetic acid (10 ml.) during 5 min. and the colourless mixture then heated under reflux for 1 hr. Dilution of the filtered solution with much water gave *methyl O-acetyltetrahydrodiketoeburicoate* which separated from methanol in colourless lustrous plates (0·14 g.), m. p. 190—191°, $[\alpha]_D^{20}$ +51° (*c*, 1·35) (Found: C, 73·0; H, 9·9. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·7%).

Dihydrodiketoeburiconic Acid.—A solution of chromic anhydride (0·07 g.) in acetic acid (2 ml.) was added dropwise in 1 hr. to dihydrodiketoeburicoic acid (0·2 g.) dissolved in acetic acid (7 ml.) kept at 40°. The mixture was then kept at 60° for 1 hr., treated with a little methanol to decompose unchanged chromic acid, and diluted with water. Crystallised from dilute methanol, the solid gave *dihydrodiketoeburiconic acid* in yellow needles (0·15 g.), m. p. 248—249°, $[\alpha]_D^{19}$ +133° (*c*, 1·03) (Found: C, 75·0; H, 9·3. $C_{31}H_{46}O_5$ requires C, 74·7; H, 9·3%). Prepared with ethereal diazomethane, the *methyl* ester was purified by means of aluminium oxide, and then from hot aqueous methanol, being obtained as an amorphous powder, $[\alpha]_D^{21}$ +116° (*c*, 0·38) (Found: C, 74·7; H, 9·6. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%).

Reduction of Eburiconic Acid.—A mixture of this acid (Part XVI, *loc. cit.*) (3·8 g.), dioxan (40 ml.), aluminium *iso*propoxide (from 1·4 g. of aluminium), and *iso*propyl alcohol (30 ml.) was heated in a distillation apparatus on the steam-bath for 8 hr.; 15 ml. of distillate were collected. The residual solution was poured into an excess of dilute hydrochloric acid, the alcohol and dioxan were removed with steam, and the solid was dried and dissolved in boiling benzene (500 ml.). On being kept this solution deposited an amorphous product (2 g.) which was dried, digested with boiling benzene (50 ml.), and then crystallised from alcohol, giving eburicoic acid, m. p. and mixed m. p. 287—288°, $[\alpha]_D^{23}$ +51° (*c*, 0·11; 4-dm. tube) (Found: C, 78·9; H, 10·8. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%), which gave the acetate, m. p. and mixed m. p. 251—253°, $[\alpha]_D^{21}$ +46° (*c*, 2·89) (Found: C, 77·3; H, 10·4. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2%).

Evaporation of the benzene liquor (500 ml.) left on separation of the crude eburicoic acid left a pale yellow gum (1·7 g.) which on acetylation with acetic anhydride (5 ml.) and pyridine (5 ml.) on the steam-bath for 3 hr. gave rise to epi-O-*acetyleburicoic acid* which was crystallised from alcohol and then methanol, forming needles, m. p. 260—261°, $[\alpha]_D^{21}$ +0·05° (*c*, 1·6) (Found: C, 76·9; H, 10·3%). Mixed with *O*-acetyleburicoic acid or with *O*-acetyldehydroeburicoic acid, it melted at about 230°; it did not depress the melting point of *epi-O*-acetyldehydroeburicoic acid. Deacetylation of this acetate gave epi*eburicoic acid*, forming needles, m. p. 257—259°, $[\alpha]_D^{21}$ +15° (*c*, 1·74), from alcohol (Found, in specimen sublimed in high vacuum: C, 78·9; H, 10·6%). This compound is considerably more soluble in chloroform, benzene, or alcohol than is eburicoic acid.

Reduction of Dehydroeburiconic Acid.—This acid (0·48 g.) was reduced with aluminium *iso*propoxide for 7 hr. and the crude product was dissolved in warm benzene (50 ml.). On being kept the cooled solution deposited a gelatinous solid which on crystallisation from alcohol gave

dehydroeburicoic acid, m. p. and mixed m. p. 286—288°, $[\alpha]_D^{24}$ +39° (*c*, 0·16; 4-dm. tube) (Found: C, 79·7; H, 10·5%); the acetate had m. p. and mixed m. p. 253—255°, $[\alpha]_D^{23}$ +62° (*c*, 0·98) (Found: C, 77·5; H, 10·0%). The benzene filtrate from the gelatinous solid was concentrated, and the residual liquor (25 ml.) kept for 2 days and, after the removal of a small amount of precipitate, evaporated. Treatment of the residue with warm acetic anhydride–pyridine gave epi-O-*acetyldehydroeburicoic acid* which separated from alcohol in needles, m. p. 262—263°, $[\alpha]_D^{23}$ +21° (*c*, 1·18), $\lambda_{max.}$ 235, 243, 252 mμ (log ε 4·17, 4·25, 4·07) (Found: C, 78·0; H, 10·0%). Mixed with *O*-acetyldehydroeburicoic acid or *O*-acetyleburicoic acid it melted at about 235°. Deacetylation of this acetate gave epi*dehydroeburicoic acid*, forming needles, m. p. 252—254°, $[\alpha]_D^{22}$ +22° (*c*, 0·2), from alcohol (Found, in specimen sublimed in high vacuum: C, 79·6; H, 10·5%).

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378. *The Orientation of Substitution in the Isomeric Thiophthens. The Synthesis of Solid Thiophthen [Thiopheno(3′ : 2′-2 : 3)thiophen].*

By FREDERICK CHALLENGER and JOHN L. HOLMES.

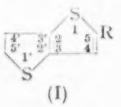
The structure of the solid thiophthen [thiopheno(3′ : 2′-2 : 3)thiophen] (I; R = H), previously determined by *X*-ray and (zero) dipole measurements, has been established by synthesis from (3-thienylthio)acetic acid by ring closure and reduction; α-(3-thienylthio)-propionic and -*n*-butyric acid similarly yield the 5-methyl and the 5-ethyl homologue. Raney nickel reduction of the methyl ketones from (I; R = H) and liquid thiophthen (II; R = H) yields octan-2-one and 5-methylheptan-2-ol respectively, thus confirming the structure of (I) and (II) and showing that substitution in the Friedel–Crafts reaction occurs in position 5.

THE two isomeric thiophthens (I; R = H) and (II; R = H) produced in the reaction between acetylene and boiling sulphur have been extensively studied during the last twenty years by one of us and his co-workers [(*a*) Challenger and Harrison, *J. Inst. Pet. Tech.*, 1935, **21**, 135; (*b*) Challenger and G. M. Gibson, *J.*, 1940, 305; (*c*) Bruce, Challenger, H. B. Gibson, and Allenby, *J. Inst. Pet.*, 1948, **34**, 226; (*d*) Challenger, Clapham, and Emmott, *ibid.*, p. 922; (*e*) Challenger and Emmott, *ibid.*, 1951, **37**, 396; (*f*) Challenger and Fishwick, *ibid.*, 1953, **39**, 320]. In (*a*) it was reported that a preliminary *X*-ray analysis kindly carried out by Dr. Bernal showed that the solid isomer possesses a plane of symmetry and is therefore represented by (I; R = H), a conclusion confirmed by Dr. F. R. Goss, who showed that it has a zero dipole moment. This physical evidence being accepted for structure (I; R = H), it was shown (*e*) that the liquid isomer must be (II; R = H) as was already almost certain from other considerations (*a*, *e*). Since then it has been found (*b*, *d*, *e*) that, for numerous electrophilic substituents, the position entered in the solid isomer is always the same. A similar conclusion was reached for liquid thiophthen. In neither case was the position determined, but later (*f*) it was shown that for the liquid isomer the position is 5, *i.e.*, adjacent to the sulphur atom. This conclusion is confirmed by further work now to be described.

The solid isomer has been synthesised. (3-Thienylthio)acetic acid (III; R = H) (Challenger, Miller, and Gibson, *J.*, 1948, 769) with hot sulphuric acid yields 4 : 5-dihydro-4-oxothiopheno(3′ : 2′-2 : 3)thiophen (IV; R = H). This compound, which was first prepared but not analysed by G. M. Gibson (Thesis, Univ. Leeds, 1939), forms a benzylidene derivative and on reduction with lithium aluminium hydride in ether yields solid thiophthen, identified by m. p. and mixed m. p. and by those of the picrate and styphnate. The corresponding 5-methyl and 5-ethyl derivatives of solid thiophthen were synthesised in a similar manner from α-(3-thienylthio)propionic acid (a liquid characterised as the amide) and α-(3-thienylthio)-*n*-butyric acid (a liquid characterised as the ethyl ester and the amide) by cyclisation to the liquids, 4 : 5-dihydro-5-methyl- and -5-ethyl-4-oxothio-

pheno(3′ : 2′-2 : 3)thiophen (IV; R = Me or Et), followed by reduction as before. The 5-methylthiophthen (I; R = Me) is a liquid forming a picrate, styphnate, and 1 : 3 : 5-trinitrobenzene derivative. The 5-ethylthiophthen (I; R = Et) is also an oil. Its picrate and 1 : 3 : 5-trinitrobenzene compound did not depress the m. p. of the corresponding derivatives of the 5-ethylthiophthen obtained (*f*) by Wolff–Kishner reduction of the corresponding 5-acetyl derivative (I; R = COMe). Reduction of this ketone with Raney nickel yields nickel sulphide and octan-2-one, characterised as semicarbazone and *p*-nitrophenylhydrazone by comparison with authentic specimens (Henderson, Henderson, and Heilbron, *Ber.*, 1914, **47**, 887). This reaction confirms the structure of (I; R = COMe), and hence of solid thiophthen itself, and also the position of substitution in the Friedel–Crafts reaction.

The methyl ketone from liquid thiophthen, *viz.*, (II; R = COMe), on reduction with Raney nickel yields 5-methylheptan-2-ol (Welt, *Ann. Chim. Phys.*, 1895, **6**, 135). No ketone could be isolated in this reaction. The alcohol was characterised as the α-naphthylamine addition product of the 3 : 5-dinitrobenzoate. No other solid derivative could be obtained. On oxidation, 5-methylheptan-2-one (Wild, *Annalen*, 1917, **414**, 118) was obtained (semicarbazone and 2 : 4-dinitrophenylhydrazone).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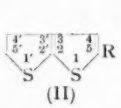
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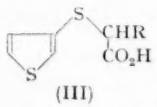
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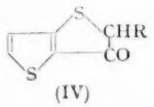
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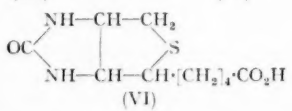
(VI)

The 5-methylheptan-2-ol required for reference was synthesised from *sec.*-butylmagnesium chloride; with gaseous formaldehyde this gave 2-methylbutan-1-ol, and the corresponding bromide by the ethyl acetoacetate synthesis gave 5-methylheptan-2-one which was then reduced with Raney nickel to the required alcohol. From the reaction with formaldehyde a high-boiling liquid, $C_{11}H_{24}O_2$, was also obtained which had no alcoholic properties but gave 2-methylbutyl bromide with aqueous hydrobromic acid. It appeared to be di-(2-methylbutyl)formal, $CH_2(O{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2Me)_2$. Pantony (Thesis, Univ. Leeds, 1948) obtained dinonylformal from the reaction between formaldehyde and octylmagnesium bromide. These formals may arise thus: $R{\cdot}MgX + CH_2O \longrightarrow R{\cdot}CH_2{\cdot}O{\cdot}MgX$; $2R{\cdot}CH_2{\cdot}OMgX + CH_2O \longrightarrow (R{\cdot}CH_2{\cdot}O)_2CH_2 + MgO + MgX_2$. A similar by-product was obtained from gaseous formaldehyde and hexylmagnesium bromide.

Challenger *et al.* (*c*) found isomeric dithienyls in the purified distillate from the interaction of acetylene and boiling sulphur. Lease and Zechmeister later (*J. Amer. Chem. Soc.*, 1947, **69**, 270, 273) isolated α-terthienyl (V) from the flowers of the Indian marigold, *Tagetus erecta* (Nat. Order *Compositæ*). Many members of this natural order contain polyacetylene derivatives; *e.g.*, Sörensen and Stene (*Annalen*, 1941, **549**, 80) isolated the diolefinic diacetylene $Me{\cdot}CH{:}CH{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CO_2Me$ from *Matricaria inodora*, a plant closely allied to the common camomile. The corresponding dihydro-derivative $Me{\cdot}CH_2{\cdot}CH_2{\cdot}C{:}C{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CO_2Me$ occurs in *Lachnophyllum gossypinum* (Wiljams, Smirnow, and Goljmow, *J. Gen. Chem. Russia*, *A*, 1935, **5**, 1195). Carlina oxide (benzyl-2-furylacetylene) occurs in the oil obtained from the roots of *Carlina acaulis* [*Cirsium acaule* (L.) Scop.].

It may be more than a coincidence that the only instance so far recorded of the occurrence of a true thiophen derivative in plants should be found in a family so many members of which contain polyacetylenes. The α-terthienyl may arise by interaction of hydrogen sulphide with a straight-chain compound containing an acetylenic–olefinic system, possibly also some methylene groups, as in the second compound cited above. Other reactions such as oxidation, decarboxylation, or dehydrogenation might be involved. It could be argued that a long-chain paraffin or fatty acid might serve equally well as the

starting point. Ring closure would, however, undoubtedly be facilitated by the presence of olefinic and acetylenic linkages.

A natural product with a modified thiophen nucleus is β-biotin (VI) which contains a tetrahydrothiophen ring with a $[CH_2]_4$·C side chain. Many natural unsaturated fatty acids, including the acetylenic derivatives erythrogenic acid CH_2:CH·C:C·$[CH_2]_4$·C:C·$[CH_2]_7$·CO_2H or CH_2:CH·$[CH_2]_4$·C:C·C:C·$[CH_2]_7$·CO_2H and tariric acid Me·$[CH_2]_{10}$·C:C·$[CH_2]_4$·CO_2H, contain this grouping and it is possible that both the heterocyclic ring and the side chain of biotin may arise from an acid of this type.

Experimental

Reductive Fission of 5-*Acetylthiopheno*(3′ : 2′-2 : 3)*thiophen.*—The ketone (3 g.) in ethyl alcohol (80 c.c.) was refluxed with an alcoholic suspension (25 c.c.) of Raney nickel for 3 hr. The solution slowly became red and finally colourless again. Next day the solid was separated and shown to evolve hydrogen sulphide with dilute acid. On removal of alcohol from the filtrate an orange oil remained which had a ketonic odour. It distilled at 70°/17 mm. (1·5 g.) and was purified *via* its sodium hydrogen sulphite compound. Decomposition with sodium carbonate and redistillation gave *n*-hexyl methyl ketone (Found : C, 74·6; H, 12·35. Calc. for $C_8H_{16}O$: C, 75·0; H, 12·5%). The semicarbazone, crystallised from alcohol, had m. p. 122·5—123° (Found : C, 58·3; H, 10·4; N, 22·9. Calc. for $C_9H_{19}ON_3$: C, 58·4; H, 10·3; N, 22·7%). The *p*-nitrophenylhydrazone, prepared in cold glacial acetic acid and crystallised from alcohol, had m. p. 92—93°. These two derivatives did not depress the m. p. of specimens prepared from authentic *n*-hexyl methyl ketone (p. 1838) which was synthesised from ethyl acetoacetate and pentyl bromide.

Reductive Fission of 5-*Acetylthiopheno*(2′ : 3′-2 : 3)*thiophen.*—The carefully purified ketone (3·8 g.) was refluxed with a suspension of Raney nickel in benzene. The solution became deep yellow and then colourless again (4 hr.). The solid was separated and washed with hot benzene. The united solvents yielded an oil, b. p. 160—162°, with an odour resembling that of octyl alcohol, and gave no precipitate with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The 3 : 5-dinitrobenzoate was an oil which did not solidify. On addition of a small quantity of α-naphthylamine a deep red solid addition product was formed which after five crystallisations from alcohol had m. p. 57—58°, and did not depress the m. p. of a specimen similarly prepared from authentic 5-methylheptan-2-ol.

Oxidation of the alcohol from the Raney nickel reaction to the corresponding ketone. 5 C.c. of a solution containing potassium dichromate (2·5 g.), water (15 c.c.), and sulphuric acid (1·5 c.c.) were heated with the alcohol (0·3 c.c.) for 30 min. and the mixture was distilled in steam. Extraction of the distillate with ether gave an oil having an odour similar to that of 5-methylheptan-2-one. The *semicarbazone*, crystallised twice from aqueous alcohol, had m. p. 131—132° not depressed by the semicarbazone of authentic 5-methylheptan-2-one (Found : C, 58·5; H, 10·2; N, 22·6. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3; N, 22·7%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 66—67° not depressed by a sample prepared from the authentic ketone (Found : C, 54·5; H, 6·4; N, 18·3. $C_{14}H_{20}O_4N_4$ requires C, 54·6; H, 6·5; N, 18·2%).

Cyclisation of (3-*Thienylthio*)*acetic Acid.*—The acid was prepared from thiophen-3-thiol and chloroacetic acid by the method of Challenger, Miller, and Gibson (*loc. cit.*), who give m. p. 50·5—51°, and of Brooks, Howard, and Wehrle (*J. Amer. Chem. Soc.*, 1950, **72**, 1289) who record m. p. 51·5—52·5° (Found : C, 41·4; H, 3·6; S, 36·5. Calc. for $C_6H_6O_2S_2$: C, 41·4; H, 3·5; S, 36·7%). On recrystallisation from water the m. p. was 52—53°. The main specimen of m. p 51—52° (10 g.) was heated on the steam-bath with sulphuric acid (100 c.c.) for 45 min. and poured on ice, and the mixture extracted with chloroform. The extract was twice washed with aqueous sodium hydrogen carbonate and dried, yielding an oil which solidified to a buff-coloured solid, m. p. 97—98 (1·24 g., 13·8%). These conditions were established as the most convenient after numerous small-scale experiments in which the proportions of the ingredients, the time, and the temperature were varied. The use of other condensing agents such as " polyphosphoric acid " (obtained by heating orthophosphoric acid at 150° for 7 days), a mixture of phosphoric oxide and orthophosphoric acid, or active alumina in boiling xylene were ineffective.

The cyclisation product [4 : 5-*dihydro*-4-*oxothiopheno*(3′ : 2′-2 : 3)*thiophen* (or the corresponding 4-hydroxy-form)] from several experiments was crystallised twice from aqueous alcohol and had m. p. 98—98·5°. G. M. Gibson (*loc. cit.*) gives m. p. 98° (Found : C, 46·3; H, 2·9; S, 40·9. $C_6H_4OS_2$ requires C, 46·2; H, 2·6; S, 41·0%). The product was soluble in

sodium hydroxide, from which it was precipitated by carbon dioxide. The *benzylidene* derivative was prepared by Auwers and Arndt's method (*Ber.*, 1909, **42**, 543) for 2-benzylidene-2 : 3-dihydro-3-oxothionaphthen. The cyclisation product (0·05 g.), benzaldehyde (5 drops), and a trace of hydrochloric acid were refluxed in alcohol for 1 hr. On cooling, silver-yellow flakes were deposited, having m. p. 141—142° unchanged on crystallisation from alcohol (Found: C, 63·5; H, 3·5; S, 26·2. $C_{13}H_8OS_2$ requires C, 63·9; H, 3·3; S, 26·2%). No semicarbazone could be obtained in aqueous alcohol.

Reduction. 4 : 5-Dihydro-4-oxothiophthen (0·2 g.) in glacial acetic acid (2 c.c.) was refluxed for 1 hr. with zinc dust (0·4 g.), and the mixture made alkaline and distilled in steam. The distillate, which had the odour of a sulphide or thiol, was extracted with ligroin. The extract gave a yellow colour and a green fluorescence with sulphuric acid, suggesting the presence of thiophthen. Evaporation left a trace of oil which solidified in ice and formed a picrate. Only minute amounts of thiophthen could have been present.

Lithium aluminium hydride (0·3 g.) was refluxed with dry ether (40 c.c.) for 10 min. 4 : 5-Dihydro-4-oxothiophthen (0·8 g.) was added, and heating continued overnight. Treatment with wet ether and then with dilute acid, separation, and evaporation of the ether left a pale red oil (0·73 g.) which solidified on cooling and was purified by steam-distillation with aqueous alkali. A white solid (0·45 g.) separated from the distillate, and a further 0·22 g. was obtained on extraction with ligroin. It had m. p. 55·5—56° and did not depress the m. p. of solid thiophthen, m. p. 55·5—56°, obtained from the sulphur–acetylene reaction in 80% yield (Found: C, 51·3; H, 3·5; S, 45·9. Calc. for $C_6H_4S_2$: C, 51·4; H, 2·9; S, 45·7%). Another preparation from 0·5 g. gave a yield of 80% of crude thiophthen, m. p. 53—55°. It was purified through the picrate, m. p. 144—145°, and decomposition with sodium carbonate in steam. The m. p. and mixed m. p. with authentic solid thiophthen was 54·5—55°.

The picrate and the styphnate, recrystallised from methyl alcohol, melted at 145—146° and 111·5—112° respectively alone and in admixture with the corresponding derivatives of solid thiophthen, m. p. 145—146° and 111·5—112° (Found, for the picrate: C, 38·6; H, 2·0; N, 11·4; S, 17·3. Calc. for $C_{12}H_7O_7N_3S_2$: C, 39·0; H, 1·9; N, 11·4; S, 17·3%. Found, for the styphnate: C, 37·5; H, 2·2; N, 10·7; S, 16·5. Calc. for $C_{12}H_7O_8N_3S_2$: C, 37·4; H, 1·9; N, 10·9; S, 16·6%).

α-(3-*Thienylthio*)*propionic Acid.*—Thiophen-3-thiol (58 g.) in a solution of sodium hydroxide (20 g.) in water (75 c.c.) was cooled in ice and stirred while α-bromopropionic acid (77 g.) and sodium hydroxide (20 g.) in water (80 c.c.) were added, the temperature being kept below 40°. Reaction was immediate, and a test portion yielded no thiol with carbon dioxide. Acidification gave an orange oil solidifying in ice to a buff-coloured mass (90 g., 90%). Recrystallisation from ligroin (b. p. 60—80°) gave a colourless solid, m. p. 77·5—78·5° (Found: C, 45·2; H, 4·5; S, 33·5. $C_7H_8O_2S_2$ requires C, 44·7; H, 4·2; S, 34·0%). The ester formed from this *acid* (Fischer–Speier) had b. p. 148—150°/23 mm.; it was shaken overnight with excess of concentrated aqueous ammonia, and the clear solution deposited the *amide*, which crystallised from water in colourless needles, m. p. 126—127° (Found: N, 7·5; S, 34·4. $C_7H_9ONS_2$ requires N, 7·5; S, 34·2%)

Cyclisation of α-(3-*Thienylthio*)*propionic Acid.*—The acid (20 g.) was cyclised by sulphuric acid (150 c.c.) at 100° for 30 min., and worked up as on p. 1839. The alkaline washings of the chloroform extract were acidified and again extracted with ether, finally yielding 4-hydroxy-5-methylthiophthen as a thick red oil (6·14 g., 30%) with a strong phenolic odour.

Synthesis of the 5-*Methyl Derivative of Solid Thiophthen.*—Lithium aluminium hydride (2 g.) was boiled for a short time with dry tetrahydrofuran (50 c.c.). The oily 4-hydroxy-5-methylthiophthen (6·14 g.) in the same solvent (50 c.c.) was slowly added. Reaction was vigorous. Next day, wet ether, dilute acid, and more ether were added as usual, and the mixed solvents separated and evaporated, leaving a red oil with a slightly phenolic odour. Distillation in steam from sodium hydroxide gave an orange oil (1·72 g., 32%) which solidified in a freezing mixture but melted again below room temperature. The whole of the oil was converted into its 1 : 3 : 5-*trinitrobenzene* derivative, which separated from methyl alcohol as yellow needles (3·3 g.), m. p. 107—108°, and 110° after two further crystallisations from the same solvent (Found: C, 42·6; H, 2·3; N, 11·6; S, 17·7. $C_{13}H_9O_6N_3S_2$ requires C, 42·5; H, 2·4; N, 11·5; S, 17·5%). This was decomposed in steam by 2N-aqueous sodium hydroxide (Challenger and Fishwick, *f*). Extraction of the distillate with ligroin gave 5-methylthiopheno(3′ : 2′-2 : 3)-thiophen as a pale yellow oil (1·4 g.) with an odour resembling that of solid thiophthen. It gave a yellow solution and a green fluorescence with sulphuric acid. The *picrate* separated from methyl alcohol in orange needles, m. p. 108—109° (Found: C, 40·8; H, 2·4; N, 11·0; S,

17·0. $C_{13}H_9O_7N_3S_2$ requires C, 40·7; H, 2·4; N, 11·0; S, 16·7%). The *styphnate* formed yellow needles, m. p. 101—102°, from methyl alcohol, in which they are very soluble (Found: C, 39·3; H, 2·3; N, 10·7; S, 16·0. $C_{13}H_9O_8N_3S_2$ requires C, 39·1; H, 2·3; N, 10·5; S, 16·1%).

α-(3-*Thienylthio*)-n-*butyric Acid.*—Thiophen-3-thiol (58 g.) was condensed with α-bromo-*n*-butyric acid (84 g.) as for the lower homologue. When the mixture had cooled to room temperature, acidification and extraction with ether yielded an orange oil which did not solidify in a freezing mixture. Any thiol was then removed with ether in presence of sodium hydrogen carbonate; acidification again gave a halogen-free oil (89 g.) which could not be solidified. It was heated to 140—150°/15 mm. to remove any α-hydroxybutyric acid and was then distilled, forming a thick, pale yellow oil, b. p. 148—150°/0·2 mm. It did not solidify during a month in a refrigerator. The ethyl ester (Fischer–Speier method) had b. p. 159—160°/19 mm. It was converted into the *amide* by concentrated aqueous ammonia. This slowly crystallised at 0°, and had m. p. 92—93° when pressed on tile and washed with ligroin. After two crystallisations from water it melted at 103—103·5° (Found: N, 7·2. $C_8H_{11}ONS_2$ requires N, 7·0%). On hydrolysis of the amide with 2N-sodium hydroxide and acidification, the acid was re-formed, but again could not be solidified. It must be assumed that α-(3-thienylthio)-*n*-butyric acid is an oil.

Cyclisation of α-(3-*Thienylthio*)-n-*butyric Acid.*—The acid (25 g.) was cyclised by sulphuric acid (150 c.c.) by 30 min.' heating on the steam-bath; the mixture was poured on ice and extracted with ether. The usual treatment yielded the cyclisation product, 5-ethyl-4-hydroxythiopheno(3′ : 2′-2 : 3)thiophen (IV; R = Et) as a red oil (6·12 g., 27%) which did not solidify. The ethereal layer containing the neutral products of the reaction gave a red oil (2·7 g.) which was not studied further.

Synthesis of the 5-*Ethyl Derivative of Solid Thiophthen* [5-*Ethylthiopheno*(3′ : 2′-2 : 3)*thiophen*].—Lithium aluminium hydride (3 g.) was refluxed with tetrahydrofuran (50 c.c.) for 10 min. and a solution of the 5-ethyl-4-hydroxy-derivative of solid thiophthen (IV; R = Et) (6·12 g.) in tetrahydrofuran (50 c.c.) was added dropwise. A very vigorous reaction occurred. The mixture was refluxed overnight and treated as in the two similar experiments. The final steam-distillate gave a yellow oil (2·9 g., 52%). A very dilute solution in ligroin gave a yellow colour and a green fluorescence with sulphuric acid. 1 : 3 : 5-Trinitrobenzene (0·22 g.) was added to the oil (0·17 g.) and the complex recrystallised twice from methyl alcohol. The yellow crystals, m. p. 85·5—86° (Found: C, 44·2; H, 3·0; N, 11·0; S, 16·7. Calc. for $C_{14}H_{11}O_6N_3S_2$: C, 44·1; H, 2·9; N, 11·0; S, 16·8%), did not depress the m. p. of the 1 : 3 : 5-trinitrobenzene derivative, m. p. 85·5—86°, of the ethylthiophthen obtained by Wolff–Kishner reduction of the methyl ketone from solid thiophthen. This was shown to be the 5-derivative (Challenger and Fishwick, *f*). The picrate, crystallised twice from methyl alcohol, had m. p. 73—73·5° (Found: N, 11·1; S, 16·5. Calc. for $C_{14}H_{11}O_7N_3S_2$: N, 10·6; S, 16·1%), not depressing the m. p. of the picrate of 5-ethylthiophthen obtained by Challenger and Fishwick as stated above.

Preparation of Reference Compounds.—5-*Methylheptan*-2-*ol.* A solution of *sec.*-butylmagnesium chloride was prepared from magnesium (27 g.), ether (400 c.c.), and the alkyl halide (117 c.c.). The reaction became violent in the early stages and some loss occurred but the experiment was continued. Gaseous formaldehyde, produced by passing nitrogen over paraformaldehyde (65 g.) at 180—200°, was then introduced through a wide delivery tube terminating about 1 cm. above the Grignard reagent. The almost solid reaction mixture was treated with ice-water (300 g.) and excess of 30% sulphuric acid, the insoluble paraformaldehyde filtered off, and the ethereal layer mixed with three ether-extracts of the aqueous liquor. Removal of solvent and fractionation of the residue yielded in addition to water two main fractions: (*a*) b. p. 125—127°, was the required 2-methylbutanol (46 g., 50%); (*b*) b. p. 80—80·5°/11 mm., the *formal*, gave no reaction with sodium and no ester odour with glacial acetic acid (Found: C, 70·0; H, 12·4. $C_{11}H_{24}O_2$ requires C, 70·0; H, 12·75. Calc. for di-2-methylbutyl ether, $C_{10}H_{22}O$: C, 76·0; H, 14·0%).

When refluxed with aqueous hydrobromic acid (*d* 1·47; 50 c.c.) the oil (*b*) (15 g.) yielded a product (12 g.; b. p. 114—115°) which was presumably 2-methylbutyl bromide. A sample prepared from 2-methylbutanol (45 g.), sulphuric acid (32 g.), and hydrobromic acid (*d* 1·47; 105 g.) had b. p. 114—116°. It was submitted to the ketone synthesis with ethyl acetoacetate. The resulting 5-methylheptan-2-one did not form a sodium hydrogen sulphite compound; it was therefore purified through the semicarbazone, m. p. 131—132° (Found: C, 58·1; H, 10·3; N, 23·2. Calc. for $C_{19}H_{19}ON_3$: C, 58·3; H, 10·3; N, 22·7%). The 2 : 4-dinitrophenylhydrazone, prepared in 2N-hydrochloric acid, formed orange crystals, m. p. 66—67° (Found: C, 54·5; H, 6·6; N, 17·5. Calc. for $C_{14}H_{20}O_4N_4$: C, 54·6; H, 6·5; N, 18·2%).

5-Methylheptan-2-ol.—The synthetic ketone (0·7 g.) in ether was added dropwise to lithium aluminium hydride (0·1 g.) in dry ether (15 c.c.) and refluxed for 30 min. Wet ether and then dilute sulphuric acid were added. The ether yielded a colourless oil, micro-b. p. 170°/757 mm. Welt (*loc. cit.*) gives b. p. 167—169°/750 mm. The hydrogen 3-nitrophthalate and the 3 : 5-dinitrobenzoate were oils and could not be crystallised but the latter readily formed an addition product with α-naphthylamine which had m. p. 57—58° after five crystallisations from alcohol (Found : C, 64·4; H, 6·3; N, 9·0. Calc. for $C_{25}H_{29}O_6N_3$: C, 64·2; H, 6·2; N, 9·0%).

We are much indebted to the Vacuum Oil Company Limited, of England, and the Socony Vacuum Oil Company Inc., of Paulsboro, New Jersey, U.S.A., for gifts of thiophen and its 3-thiol derivative and to the Ministry of Education for an F.E.T.S. grant to J. L. H.

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379. *Triterpenoids. Part XII.* The Lanosterol Analogue of Provitamin D_3.*

By D. H. R. BARTON and B. R. THOMAS.

7-Ketolanostan-3β-yl acetate has been converted by selenium dioxide into 7-ketolanost-5-en-3β-yl acetate and thence by lithium aluminium hydride reduction followed by acid-catalysed dehydration into lanosta-5 : 7-dien-3β-ol. The stereochemistry of $C_{(7)}$ in lanostanol derivatives has been elucidated. Some miscellaneous reactions have been studied.

THE solution of the constitutional and stereochemical problems posed by the lanostadienol (lanosterol) molecule, suggests that lanosterol analogues of physiologically active steroids might well prove of interest (see Barton, Proc. Ciba Conference on Adrenocortical Hormones, July, 1952). We now wish to report (for preliminary communication see Barton and Thomas, *Chem. and Ind.*, 1953, 172) the preparation of the lanosterol analogue (I; R = H) of provitamin D_3 (7-dehydrocholesterol) (II), as well as some related observations bearing on the chemistry of lanosterol.

7-Ketolanost-8-en-3β-yl acetate (III) (Birchenough and McGhie, *J.*, 1950, 1249; Cavalla and McGhie, *J.*, 1951, 744; and references there cited) was reduced by lithium in liquid ammonia (cf. Birch, *J.*, 1944, 430, and subsequent papers) to 7-ketolanostan-3β-yl acetate (IV; R = Ac), identical with the ketone obtained previously (Barton, Fawcett, and Thomas, *J.*, 1951, 3147) by the action of perbenzoic acid on lanost-7-en-3β-yl acetate (V). In the latter the configuration at $C_{(9)}$ must be the more stable α, since it is prepared under equilibrating conditions. The configuration at $C_{(8)}$ in (IV; R = Ac) must be β- because, as shown by its stability towards attempted isomerisation by alkali (see Experimental section), it represents the more stable arrangement.

Oxidation of (IV; R = Ac) by selenium dioxide in acetic acid gave 7-ketolanost-5-en-3β-yl acetate (VI) in excellent yield. Lithium aluminium hydride reduction of (VI), followed by controlled treatment with aqueous dioxan–sulphuric acid and then acetylation or benzoylation, gave, respectively, lanosta-5 : 7-dien-3β-yl acetate (I; R = Ac) or benzoate (I; R = Bz). From these operations 7-ketolanostan-3β-yl acetate (IV; R = Ac) or benzoate (IV; R = Bz) was also isolated. The latter was identical with a specimen prepared directly from the corresponding acetate. Alkaline hydrolysis of (I; R = Ac) gave lanosta-5 : 7-dien-3β-ol (I; R = H).

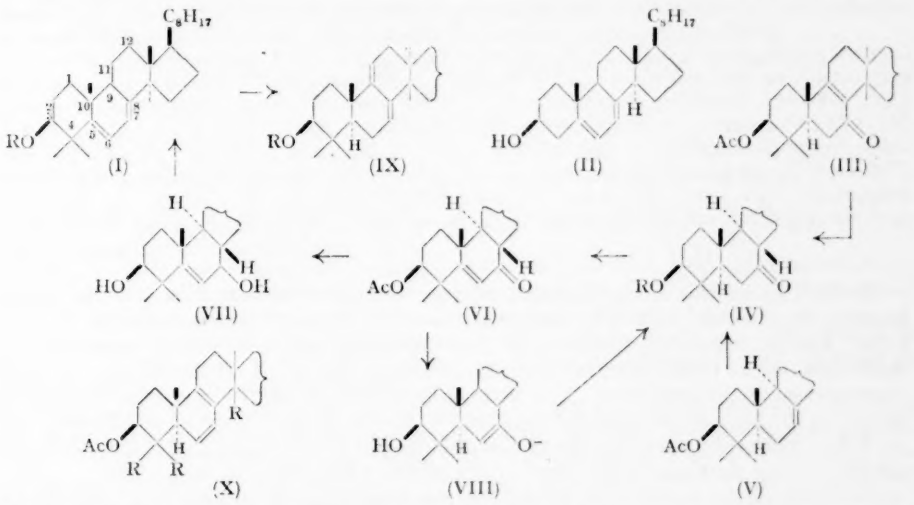
The mechanism for the re-formation of (IV) in the lithium aluminium hydride reduction was studied further. The crude reduction product showed a saturated ketone band in the infra-red at 1705 $cm.^{-1}$. Acetylation of the crude product and chromatography without acid treatment gave (IV; R = Ac). It can be concluded that (VI) is attacked by lithium aluminium hydride in two ways : (*a*) addition of hydride ion at $C_{(7)}$ produces the allylic alcohol (VII) [subsequently transformed by acid-catalysed dehydration into (I; R = H)]

* Part XI, *J.*, 1953, 1419.

and (*b*) addition of hydride ion at $C_{(5)}$ with consequent electronic displacements produces the anion (VIII) which resists further reduction.

The constitution assigned to (I) is supported by the following evidence. (i) Treatment of (I; R = Ac) with hydrogen chloride in chloroform gave lanosta-7 : 9(11)-dien-3β-yl acetate (IX; R = Ac). (ii) In the infra-red (I; R = Ac) showed bands at **1732** and **1238** cm.$^{-1}$ due to the acetate residue, and at **1640**, **830** and **810** cm.$^{-1}$, due to $-CH{=}C<$. This spectrum excludes the alternative formulation (X; R = Me) which is otherwise consistent with the ultra-violet absorption spectrum and the mode of formation. Furthermore the analogous *iso*dehydrocholesterol acetate (X; R = H) (Windaus, Linsert, and Eckhardt, *Annalen*, **1938**, **534**, 22) showed bands at **1735** and **1240** cm.$^{-1}$ due to the acetate residue and at **718** cm.$^{-1}$. The last band is characteristic of *cis*-$CH{=}CH-$ and is entirely absent in the spectrum of (I; R = Ac). (iii) The molecular-rotation differences for (I; R = H) on acetylation and benzoylation are **+131** and **+351** respectively. These values are comparable with those (**+110** and **+178** respectively; see Barton and Cox, *J.*, **1948**, 783) recorded for acylation of ergosterol, but are in contrast to the figures (+22 and +52 respectively; see Barton, *J.*, **1945**, 813) for *iso*dehydrocholesterol.

The ready availability of 7-ketolanostan-3β-ol prompted us to investigate a number of derivatives. Oxidation with chromic acid gave lanostane-3 : 7-dione * (XI), also obtained by prolonged reduction of 7-ketolanost-8-en-3β-yl acetate by lithium in liquid ammonia followed by chromic acid oxidation of the product. Reduction of 7-ketolanostan-3β-yl acetate (IV; R = Ac) by lithium aluminium hydride afforded lanostane-3β : 7β-diol (XII; R = H), further characterised as the diacetate (XII; R = Ac). This diol was also obtained when 3 : 7-diketolanostane was reduced with sodium and propanol.



Hydrogenation of 3 : 7-diketolanostane in ethyl acetate solution gave 7-ketolanostan-3β-ol characterised as the acetate (IV; R = Ac). Whilst (IV; R = H) was not hydrogenated further in this medium, corresponding hydrogenation of (IV; R = Ac) in ethyl acetate–acetic acid furnished lanostane-3β : 7α-diol 3-acetate (XIII; R = Ac, R′ = H) further characterised by hydrolysis to the diol (XIII; R = R′ = H) and by acetylation to the diacetate (XIII; R = R′ = Ac).

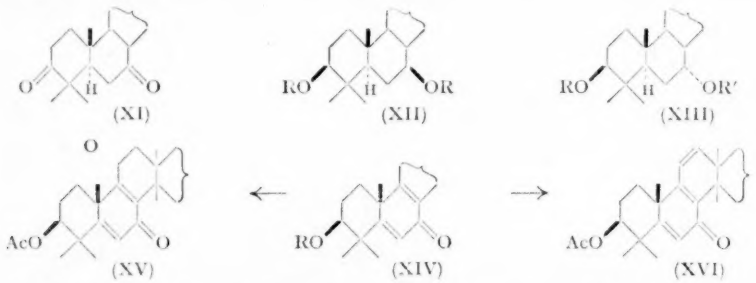
The configurations assigned at $C_{(7)}$ in these compounds are based on the following considerations. (i) The equatorial (β) character of the diol produced by sodium and propanol reduction follows from the method of preparation (Barton, *Experientia*, **1950**, **6**, 316). (ii) The molecular-rotation difference on going from (XII; R = Ac) to (XIII;

* We understand that this compound has also been prepared independently by Dr. J. F. McGhie and his collaborators. We thank Dr. McGhie cordially for this information.

R = R′ = Ac) was −280. The corresponding difference in *trans*-AB saturated steroids is −351 (see Barton and Klyne, *Chem. and Ind.*, 1948, 755).

In confirmation of these configurational assignments treatment of lanostane-3β : 7α-diol 3-acetate with phosphorus oxychloride and pyridine gave, by smooth *trans*-elimination of polar 7α-OH and polar 8β-H, lanost-7-en-3β-yl acetate (V) (cf. the corresponding reaction in the cholestane series; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503; Fieser, Fieser, and Chakravarti, *ibid.*, 1949, **71**, 2226; Heymann and Fieser, *Helv. Chim. Acta*, 1952, **35**, 631).

As a by-product in the preparation of 7-ketolanost-8-en-3β-yl acetate we have isolated 7-ketolanosta-5 : 8-dien-3β-yl acetate (XIV; R = Ac). This was further characterised by hydrolysis to the alcohol (XIV; R = H). The constitution assigned is based on the following evidence. (*a*) The ultra-violet absorption is that of an αβ-unsaturated ketone. (*b*) The infra-red spectrum shows bands at 1738 and 1236 cm.$^{-1}$ due to the acetate residue, and at 1646 cm.$^{-1}$ indicative of a carbonyl group conjugated with two double bonds. In comparison 7-ketolanost-8-en-3β-yl acetate (III) showed bands at 1736 and 1242 cm.$^{-1}$ due to the acetate residue, and at 1662 cm.$^{-1}$ corresponding to a singly conjugated carbonyl group. (*c*) Oxidation by chromic acid afforded in good yield 7 : 11-diketolanosta-5 : 8-dien-3β-yl acetate (XV) (Voser, Montavon, Günthard, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 1893). (*d*) Oxidation by selenium dioxide in acetic acid furnished 7-ketolanosta-5 : 8 : 11-trien-3β-yl acetate (XVI) (Birchenough and McGhie, *J.*, 1950, 1249). Treatment with zinc dust and acetic acid afforded an isomeric phenol, the constitution of which was not investigated further.



In Part IX of this series (*J.*, 1953, 571) we described the reduction of 7 : 11-diketolanostan-3β-yl acetate by sodium and propanol to the triequatorial lanostane-3β : 7β : 11α-triol. The corresponding reaction in the ergosterol series has now been effected. Reduction of 7 : 11-diketoergost-22-en-3β-yl acetate gave, as main product, a triol, characterised as the triacetate. The latter is formulated as 3β : 7β : 11α-triacetoxyergost-22-ene on the basis of its mode of formation (cf. Barton, *loc. cit.*; Barton and Rosenfelder, *J.*, 1951, 1048) and because its observed molecular rotation is in good agreement with that calculated from standard Tables (Barton and Klyne, *Chem. and Ind.*, 1948, 755).

In Part VII of this series (*J.*, 1952, 2339) the preparation of *inter al.*, 7 : 11 : 12-triketo-7*a*-aza-B-homolanostan-3β-yl acetate was described. Falco, Voser, Jeger, and Ruzicka recently (*Helv. Chim. Acta*, 1952, **35**, 2430) queried the m. p. (269—273°) which we recorded. Our m. p. is correct as given when taken in a Pyrex-glass capillary. In a soda-glass capillary the m. p. becomes indefinite and may be as low as 230—240°. We cannot confirm however the m. p. (208—210°) given by Falco *et al.*, which may represent therefore a different crystalline modification. The rotations recorded are in agreement.

Experimental

For general experimental directions see Part VII (*J.*, 1952, 2339). Infra-red spectra, in carbon disulphide solution, were kindly determined by Dr. J. E. Page (of Messrs. Glaxo Laboratories Ltd.) using a Perkin–Elmer double-beam instrument. $[\alpha]_D$ are in $CHCl_3$. Ultra-violet absorption spectra refer to ethanol solutions.

7-Ketolanostan-3β-ol.—7-Ketolanost-8-en-3β-yl acetate (3 g.) in sodium-dried ether (200 ml.) was added to liquid ammonia (300 ml.) during 15 min. At the same time lithium (300 mg.) was added in small pieces so as to maintain the blue colour of the solution. After a further 5 min. *tert.*-butanol in ether (20 ml.; 50%) was run in, the solution was diluted with ether, and water added. After removal of the ether *in vacuo* the product was chromatographed over alumina. Elution with 1 : 1 benzene–ether afforded 7-ketolanostan-3β-yl acetate, m. p. (from ethanol) 172°, $[\alpha]_D$ +36° (*c*, 2·4), undepressed in m. p. on admixture with an authentic specimen (Barton, Fawcett, and Thomas, *loc. cit.*). Alkaline hydrolysis of the acetate gave *7-ketolanostan-3β-ol*, m. p. (from methanol) 171—173°, $[\alpha]_D$ +28° (*c*, 1·7) (Found: C, 80·8; H, 11·75. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%), depressed in m. p. on admixture with the parent acetate, but reconverted thereinto on acetylation (m. p. and mixed m. p.).

7-Ketolanost-5-en-3β-yl Acetate.—7-Ketolanostan-3β-yl acetate (500 mg.) and selenium dioxide (500 mg.) were refluxed in "AnalaR" acetic acid (25 ml.) for 4 hr. The product was crystallised from methanol, to give *7-ketolanost-5-en-3β-yl acetate* (400 mg.), m. p. 188—189°, $[\alpha]_D$ −37° (*c*, 1·1), $\lambda_{max.}$ 238 mμ (ε = 12,500) (Found: C, 79·0; H, 10·85. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Lanosta-5 : 7-dien-3β-ol.—7-Ketolanost-5-en-3β-yl acetate (400 mg.) in sodium-dried ether (20 ml.) was refluxed with lithium aluminium hydride (100 mg.) in the same solvent (20 ml.) for 2 hr. The product was dissolved in aqueous dioxan [20 ml.; 20% (v/v) of water] containing 5% (w/v) of sulphuric acid and kept at 50° for 2 hr. Preliminary experiments with spectroscopic control had shown that these were the optimum conditions. The product was acetylated and chromatographed. Elution with 1 : 1 light petroleum–benzene gave *lanosta-5 : 7-dien-3β-yl acetate* (55 mg.), m. p. (from chloroform–methanol) 134—136°, $[\alpha]_D$ −115° (*c*, 0·9), $\lambda_{max.}$ 273 mμ (ε = 11,000) (Found: C, 82·05; H, 11·1. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Elution with benzene afforded 7-ketolanostan-3β-yl acetate identified by m. p. and mixed m. p. This acetate was also isolated when the crude lithium aluminium hydride reduction product was acetylated and chromatographed (without sulphuric acid treatment).

In a further experiment the crude product from the acid-catalysed dehydration (180 mg.) was benzoylated and then chromatographed. Elution with 1 : 4 benzene–light petroleum gave *lanosta-5 : 7-dien-3β-yl benzoate* (60 mg.), m. p. (from chloroform–methanol) 186—187°, $[\alpha]_D$ −60° (*c*, 1·2), $\lambda_{max.}$ 230 and 273 mμ (ε = 16,000 and 14,000 respectively) (Found: C, 83·4; H, 10·15. $C_{37}H_{54}O_2$ requires C, 83·7; H, 10·25%). Elution with 1 : 1 benzene–light petroleum furnished *7-ketolanostan-3β-yl benzoate* (70 mg.), m. p. (from chloroform–methanol) 246—247°, $[\alpha]_D$ +50° (*c*, 1·1), $\lambda_{max.}$ 230 mμ (ε = 15,000) (Found: C, 81·1; H, 10·25. $C_{37}H_{56}O_3$ requires C, 80·95; H, 10·3%), identical (m. p. and mixed m. p.) with a specimen prepared directly from the corresponding acetate (see above).

Alkaline hydrolysis of lanosta-5 : 7-dien-3β-yl acetate gave the corresponding *alcohol*, m. p. (from methanol) 137—138° (after drying *in vacuo* at 80°), $[\alpha]_D$ −157° (*c*, 0·7), $\lambda_{max.}$ 274 mμ (ε = 11,500) (Found: C, 83·95; H, 11·6. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%).

Treatment of lanosta-5 : 7-dien-3β-yl acetate (5 mg.) in chloroform (5 ml.) with a stream of hydrogen chloride gas for 10 min. gave lanosta-7 : 9(11)-dien-3β-yl acetate (3 mg.), identified by m. p., mixed m. p., and absorption spectrum.

Lanostane-3 : 7-dione.—7-Ketolanost-8-en-3β-yl acetate (2·6 g.) was reduced with lithium in liquid ammonia as detailed above, except that a large excess of lithium was used and the reaction mixture was stirred for 1 hr. before addition of the *tert.*-butanol–ether solution. The reaction product in acetic acid was oxidised with chromium trioxide and then chromatographed (elution with benzene) to give *lanostane-3 : 7-dione* (850 mg.), m. p. (from methanol) 130—131°, $[\alpha]_D$ +5° (*c*, 2·4), $\lambda_{max.}$ 293 mμ (ε = 75) (Found: C, 81·0; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). This dione was also prepared by chromic acid oxidation of 7-ketolanostan-3β-ol (see above), the identity being confirmed by m. p. and mixed m. p. Lanostane-3 : 7-dione was recovered unchanged (m. p. and mixed m. p.) on refluxing with 5% methanolic potassium hydroxide solution for 30 min.

Lanostane-3 : 7-dione (35 mg.) in ethyl acetate (25 ml.) was hydrogenated over a platinum catalyst for 1 hr. The product was chromatographed over alumina. Elution with benzene afforded unchanged starting material, but elution with 1 : 1 benzene–methanol gave 7-keto-lanostan-3β-ol, characterised by conversion into the acetate (180 mg.) and identified by m. p. and mixed m. p.

Lanostane-3β : 7β-diol.—7-Ketolanostan-3β-yl acetate (100 mg.) was reduced by lithium aluminium hydride and the product acetylated. Chromatography over alumina (elution with 1 : 9 ether–benzene) afforded *lanostane-3β : 7β-diol diacetate* (70 mg.), m. p. (from methanol)

185—186°, $[\alpha]_D$ +33° (*c*, 0·7) (Found: C, 76·6; H, 10·8. $C_{34}H_{58}O_4$ requires C, 76·95; H, 11·0%). Alkaline hydrolysis gave *lanostane*-3β : 7β-*diol*, m. p. (from methanol) 204—206°, $[\alpha]_D$ +37° (*c*, 2·4) (Found: C, 80·1; H, 12·15. $C_{30}H_{54}O_2$ requires C, 80·65; H, 12·2%).

Lanostane-3β : 7β-diol diacetate (70 mg.) was also obtained when lanostane-3 : 7-dione (100 mg.) was reduced with sodium and propanol, and the product acetylated. The identification was by m. p. and mixed m. p.

Lanostane-3β : 7α-*diol*.—7-Ketolanostan-3β-yl acetate (500 mg.) in 1 : 1 ethyl acetate–acetic acid (50 ml.) was hydrogenated over a platinum catalyst for 36 hr. The product was chromatographed over alumina. Elution with 99 : 1 benzene–ether afforded unchanged 7-ketolanostan-3β-yl acetate; elution with 9 : 1 benzene–ether gave *lanostane*-3β : 7α-*diol* 3-*acetate* (280 mg.), m. p. (from methanol) 205—206°, $[\alpha]_D$ +14° (*c*, 1·2), no absorption at 280 mμ (Found: C, 79·0; H, 11·8. $C_{32}H_{56}O_3$ requires C, 78·65; H, 11·55%). 7-Ketolanostan-3β-yl acetate was recovered unchanged after attempted hydrogenation (20 hr.' shaking) over platinum in ethyl acetate.

Acetylation of the monoacetate by pyridine–acetic anhydride on the steam-bath for 1 hr. gave *lanostane*-3β : 7α-*diol diacetate*, m. p. (from ethyl acetate–methanol) 167—168°, $[\alpha]_D$ −20° (*c*, 1·1) (Found: C, 76·6; H, 10·85. $C_{34}H_{58}O_4$ requires C, 76·95; H, 11·0%).

Alkaline hydrolysis of the monoacetate afforded *lanostane*-3β : 7α-*diol*, m. p. (from methanol) 163—165° after sintering at 158°, $[\alpha]_D$ +5° (*c*, 1·8) (Found: C, 78·85; H, 11·95. $C_{30}H_{54}O_2,0{\cdot}5CH_3{\cdot}OH$ requires C, 79·2; H, 12·2%).

Dehydration of Lanostane-3β : 7α-*diol* 3-*Acetate*.—The monoacetate (70 mg.) was heated on the steam-bath with dry pyridine (5 ml.) and redistilled phosphorus oxychloride (1 ml.). The product, purified by chromatography and recrystallisation from chloroform–methanol, was identified as pure lanost-7-en-3β-yl acetate (35 mg.) by m. p., mixed m. p. (for authentic specimen, see Barton, Fawcett, and Thomas, *loc. cit.*), and rotation {$[\alpha]_D$ +25° (*c*, 2·2)}.

7-*Ketolanosta*-5 : 8-*dien*-3β-*ol*.—The 7-ketolanost-8-en-3β-yl acetate used in the above experiments was purified by chromatography over alumina. The tail fractions from the chromatogram were crystallised from methanol, to give 7-*ketolanosta*-5 : 8-*dien*-3β-*yl acetate*, m. p. 186—188°, $[\alpha]_D$ −14° (*c*, 2·5), $\lambda_{max.}$ 249 mμ (ε = 13,500) (Found: C, 79·25; H, 10·9. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). Alkaline hydrolysis afforded 7-*ketolanosta*-5 : 8-*dien*-3β-*ol*, m. p. (from aqueous methanol) 170° (after drying *in vacuo* at 80°), $[\alpha]_D$ −14° (*c*, 2·0) (Found: C, 81·3; H, 10·9. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

7-Ketolanosta-5 : 8-dien-3β-yl acetate (100 mg.) in "AnalaR" acetic acid (10 ml.) was oxidised with chromium trioxide (40 mg.) in a little aqueous acetic acid at 85° for 1 hr. The product was chromatographed over alumina. Elution with benzene afforded 7 : 11-diketolanosta-5 : 8-dien-3β-yl acetate (45 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +69° (*c*, 1·7)}, and absorption spectrum [$\lambda_{max.}$ 272 mμ (ε = 12,500)].

7-Ketolanosta-5 : 8-dien-3β-yl acetate (30 mg.) in "AnalaR" acetic acid (10 ml.) was refluxed with selenium dioxide (30 mg.) for 3 hr. The product was crystallised from methanol, to give 7-ketolanosta-5 : 8 : 11-trien-3β-yl acetate (15 mg.), identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +66° (*c*, 1·0)}, and absorption spectrum [$\lambda_{max.}$ 258 and 326 mμ (ε = 8500 and 8500 respectively)].

7-Ketolanosta-5 : 8-dien-3β-yl acetate (100 mg.) in "AnalaR" acetic acid (10 ml.) was refluxed with zinc dust for 2 hr. The product was crystallised from methanol, to give a *phenol*, m. p. 212—214°, $[\alpha]_D$ +51° (*c*, 1·1), $\lambda_{max.}$ 287 mμ (ε = 3500), changed to $\lambda_{max.}$ 302 mμ (ε = 3500) on addition of ethanolic potassium hydroxide (Found: C, 79·9; H, 10·1. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

Reduction of 7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate* (with C. S. Barnes).—The diketone (1·0 g.) in refluxing propanol (10 ml.) was reduced by the addition of sodium until the solution was saturated. After acetylation the product was chromatographed over alumina. Elution with 1 : 1 benzene–light petroleum furnished 3β : 7β : 11α-*triacetoxyergost*-22-*ene* (350 mg.), m. p. (from chloroform–methanol) 159—161°, $[\alpha]_D$ −51° (*c*, 3·2), $[M]_D$ −279° {calculated $[M]_D$ according to the standard tables of Barton and Klyne (*loc. cit.*) −294°} (Found: C, 73·25; H, 9·8. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·75%). The compound showed no ketonic band in either the ultra-violet or the infra-red region.

Elution with benzene and benzene–ether gave mixtures which were not investigated further. Elution with ether furnished a fraction (50 mg.) which had m. p. (from chloroform–methanol) 159—161° (depressed by 30° on admixture with the 3β : 7β : 11α-triacetate), $[\alpha]_D$ −10° (*c*, 2·4) $[M]_D$ −56° (calculated for 3β : 7α : 11α-triacetoxyergost-22-ene $[M]_D$ +57°) (Found: C, 72·7; H, 9·45%). This fraction showed no ketonic band in either the ultra-violet

or the infra-red region. The fraction is almost certainly enriched in the 3β : 7α : 11α-triacetate, but there was insufficient material for further purification.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited, for financial assistance. We are also grateful to Messrs. Glaxo Laboratories Ltd. for gifts of chemicals, and to the International Wool Secretariat for a Post-doctorate Fellowship made available to one of us (B. R. T.).

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, February 24th,* 1953.]

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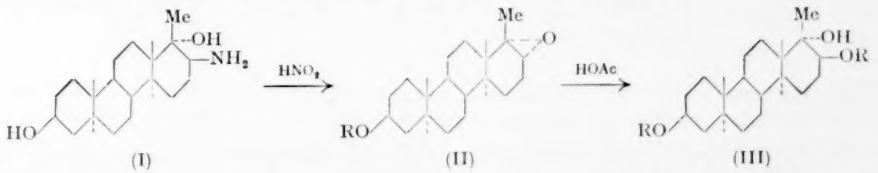
380. *Steroids and Walden Inversion. Part X.* The Reconversion* D-*Homosteroids into Steroids.*

By R. J. W. CREMLYN, D. L. GARMAISE, and C. W. SHOPPEE.

On the basis of stereoelectronic considerations the smooth conversion of 17α-amino-17*a*β-hydroxy-17*a*-methyl-D-homoandrost-5-en-3β-ol (IX) by deamination into 17-*iso*pregnenolone has been achieved. The 17*a*-epimeride (VII) of (IX) by deamination gives 17-*iso*pregnenolone accompanied by relatively much of the 17α : 17*a*α-epoxide (X). These results suggest that a synchronous process involving a diazonium ion: $\bar{O}-\overset{R}{\overset{\curvearrowright}{C}}-C\overset{\curvearrowright}{-}\overset{+}{N}\equiv N$ rather than a process involving a carbonium ion: $\bar{O}-CR-C\overset{\curvearrowright}{-}\overset{+}{N}\equiv N \longrightarrow \bar{O}-\overset{R}{\overset{\curvearrowright}{C}}-C$ may be operative in pinacolic deamination in cyclic systems.

DEAMINATION with nitrous acid of the dihydroxy-amine (I) was found by Ruzicka and Meldahl (*Helv. Chim. Acta*, **1941**, **24**, 1321) to give an epoxide (II; R = H). The structure of this epoxide was proved by acetolysis of its acetate (II; R = Ac) by Ruzicka and Meldahl to a triol diacetate (III; R = Ac) hydrolysed by alkali to a triol (III; R = H) which was obtained by Ruzicka, Gätzi, and Reichstein (*Helv. Chim. Acta*, **1939**, **22**, 676) and by Stavely (*J. Amer. Chem. Soc.*, **1941**, **63**, 3127); the structure of the triol was first correctly given by Shoppee and Prins (*Helv. Chim. Acta*, **1943**, **26**, 201).



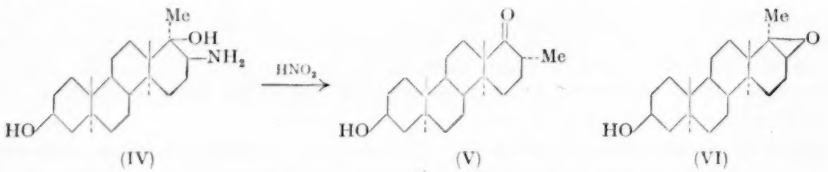
(I) (II) (III)

During a study of methods for the conversion of D-homosteroids into steroids, the 17*a*-epimeric dihydroxy-amine (IV) was found by Prins and Shoppee (*J.*, **1946**, 494) to give a substance isomeric with (II; R = H), which they regarded as the 17β : 17*a*β-epoxide (VI) because it appeared in the non-ketonic fraction on Girard separation, but this substance has since been shown by Klyne (*Nature*, 1950, **166**, 559) to be identical with the 3β-hydroxy-17*a*-ketone (V) (≡ "uranolone") of Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1938, **60**, 2719).

The dihydroxy-amines (I) and (IV) were each obtained by catalytic hydrogenation, with platinum and acetic acid, of the oximes of the corresponding dihydroxy-ketones. Examples of the reduction of oximes may be found in the recent work of McNiven and Read (*J.*, 1952, 153) on the isomeric menthylamines. It is clear from the behaviour of the menthylammonium hydroxides on decomposition that the amines produced by reduction of the oximes with sodium and ethanol have equatorial amino-groups, whilst those produced by catalytic hydrogenation have polar amino-groups. It therefore is

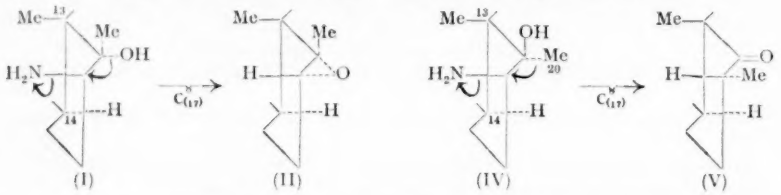
* Part IX, *J.*, 1953, 241; Part XI, *J.*, 1953, 1709.

highly probable that the amino-groups in the D-homohydroxy-amines are polar (*i.e.*, 17β) as in (I) and (IV).



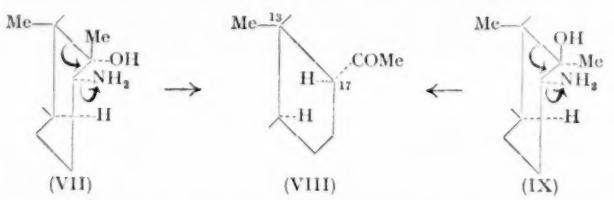
(IV) (V) (VI)

The rearrangement (I ⟶ II) may now be represented as follows (cf. Klyne and Shoppee, *Chem. and Ind.*, 1952, 470). The polar hydroxyl group (17*aα*) and the polar amino-group (17β) afford a transition state with four coplanar centres [O, $C_{(17a)}$, $C_{(17)}$, N] leading with inversion at $C_{(17)}$ to the 17α : 17*aα*-epoxide (II). Similarly, the rearrangement (IV ⟶ V) may be represented by interaction of the polar methyl group [17*aα*] and the polar amino-group [17β] to furnish a transition state with four coplanar centres [$C_{(20)}$, $C_{(17a)}$, $C_{(17)}$, N] leading with inversion at $C_{(17)}$ to the 17α-methyl ketone (V).



(I) (II) (IV) (V)

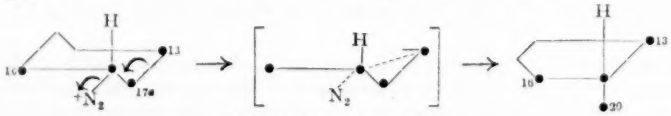
These stereo-electronic considerations suggest that 17-epimeric dihydroxy-17α-amines (VII, IX; NH_2 equitorial) should undergo deamination with rearrangement accompanied by ring-decrease to give 17α-pregnan-20-ones (VIII). In either case a transition state involving the four coplanar centres [$C_{(13)}$, $C_{(17a)}$, $C_{(17)}$, N] should lead with retention of configuration * at $C_{(17)}$ to the ketone [" 17-*iso*pregnenolone "] (VIII).†



(VII) (VIII) (IX)

The 17*a*-epimeric dihydroxy-17α-amines (VII, IX) were prepared by reduction of the oximes of the corresponding 17-ketones with sodium and propanol; they were carefully purified and appeared homogeneous. Deamination of (IX) gave, as sole crystalline product

* As a consequence of the formation of a linear transition state, there is a *formal* inversion of configuration at $C_{(17)}$ in the transformation of both (VII) and (IX) into the ketone (VIII); there is, however, no *actual* inversion of configuration at $C_{(17)}$ because the hydrogen atom attached to $C_{(17)}$ does not cross the plane of ring D:

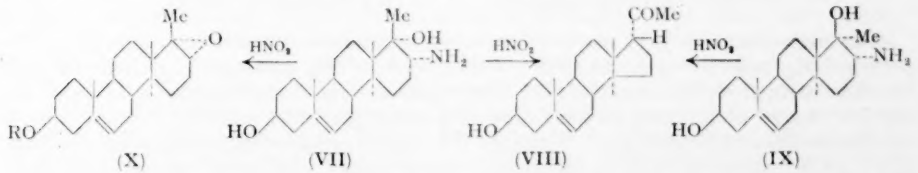


Linear transition state

(D-Homosteroid $C_{(17a)}$ becomes steroid $C_{(20)}$.)

† Since this paper was written our attention has been directed to the work of McCasland (*J. Amer. Chem. Soc.*, 1951, **73**, 2293) on the deamination of the *cis*- and *trans*-2-hydroxy*cyclo*hexylamines which each exist as a non-resolvable mixture of two antimeric equatorial-polar conformations. In our case all four conformations correspond to individual substances.

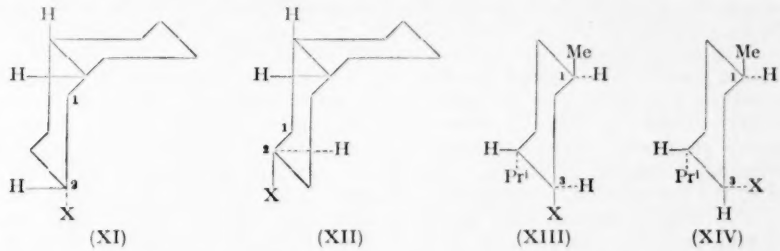
and in good yield, 17-*iso*pregnenolone (VIII), m. p. 172—173°, $[\alpha]_D$ −138° {Butenandt and Fleischer (*Ber.*, 1937, **70**, 96) give m. p. 172°, $[\alpha]_D$ −140°}, characterised as the acetate, m. p. 171°.



(X) (VII) (VIII) (IX)

By contrast, deamination of (VII) led to a mixture separated by use of Girard's reagent T into a relatively small quantity of 17-*iso*pregnenolone (VIII) and a relatively large amount of the 17α : 17aα-epoxide (X; R = H); the latter, as the acetate, by hydrogenation gave a product, m. p. 161°, which appeared to correspond with the epoxide (II; R = Ac).

It has been shown by Ingold, Hughes, *et al.* (*Nature*, 1950, **166**, 178) on the basis of configurational studies that, for simple aliphatic primary amines, the last steps of deamination must have the form of a S_N1 process involving a carbonium-ion intermediate: $R{\cdot}NH_2 \longrightarrow R{\cdot}\overset{+}{N}{\equiv}N \longrightarrow \overset{+}{R}$. It appears that in cyclic systems molecular geometry may confer importance upon the earlier diazonium-ion intermediate. Thus the epimeric *cis*-2-decalylamines (XI, XII; X = NH_2, equatorial in both epimers *) undergo deamination to give the epimeric *cis*-2-decalols (XI, XII; X = OH) with almost complete retention of configuration (Dauben and Hoerger, *J. Amer. Chem. Soc.*, 1951, **73**, 1504); these observations seem to exclude a carbonium-ion intermediate. On the other hand, whilst (−)-



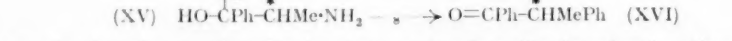
(XI) (XII) (XIII) (XIV)

menthylamine (XIII; X = NH_2, equatorial) is deaminated to (−)-menthol (XIII; X = OH) with retention of configuration and so presumably without intervention of a carbonium ion, (+)-*neo*menthylamine (XIV; X = NH_2, polar) gives (+)-*p*-menth-3-ene (elimination) (cf. Birch, *Ann. Reports*, 1950, **47**, 192), accompanied by *p*-menthan-4-ol (rearrangement), products which suggest the formation of a carbonium ion.

Ingold and Shoppee (*J.*, 1928, 365) originally classified pinacolic deamination of α-hydroxy-amines and Wagner rearrangements with elimination reactions; it is now known that the Wagner rearrangement is a form of unimolecular nucleophilic substitution or elimination [S_N1, $E1$] involving the carbonium ions $R{-}C_\alpha{-}C_\beta^+$ and $^+C_\alpha{-}C_\beta{-}R$ or their synartetic hybrid (Hughes, Ingold, *et al.*, *Nature*, 1951, **168**, 65). Whilst Ingold (*Ann. Reports*, 1928, **25**, 133) emphasised the importance of a carbonium-ion intermediate: $\bar{O}{-}C_\alpha R{-}C_\beta{-}\overset{+}{N}{\equiv}N \longrightarrow \bar{O}{-}\overset{R}{C_\alpha}{-}\overset{+}{C_\beta} \longrightarrow \bar{O}{-}\overset{+}{C_\alpha}{-}C_\beta R$, Shoppee (*Proc. Leeds Phil. Soc.*, 1928, **1**, 301) suggested the operation of a synchronous process involving a diazonium ion: $\bar{O}{-}\overset{R}{C_\alpha}{-}C_\beta{-}\overset{+}{N}{\equiv}N \longrightarrow \bar{O}{-}\overset{+}{C_\alpha}{-}C_\beta R$. Only the latter mechanism appears able to account for the preservation of optical activity, with inversion of configuration, in the pinacolic

* *cis*-Decalin exists in two equivalent conformations inter-convertible by transformation of all equatorial into polar bonds and *vice versa* (Hassel, *Research*, 1950, **3**, 504).

deamination of (−)-2-amino-1 : 1-diphenylpropanol (XV) to (+)-methyldeoxybenzoin (XVI) (McKenzie, Roger, and Wills, *J.*, 1926, 779).



If a carbonium ion is of major importance in pinacolic deamination then (I; α-OH, polar/β-NH_2, polar; *trans*) and (VII; α-OH, polar/α-NH_2, equatorial; *cis*) should yield the same main product(s), and the 17α : 17*a*α-epoxide (X) is formed from both (I) and (VII), the 17*a*-oxygen atom being geometrically favourably placed to maintain configuration in an intermediate carbonium ion. Similarly (IV; β-OH, equatorial/β-NH_2, polar; *cis*) and (IX; β-OH, equatorial/α-NH_2, equatorial: *trans*) should yield some common product(s). But now the oxygen atom is geometrically unfavourably placed for intervention and the methyl group has no electrons available to participate in maintaining configuration in a carbonium ion. Not only is no common product formed but each α-hydroxy-amine gives the product appropriate to the geometry of a precursor diazonium ion. This result suggests that in pinacolic deamination in polycyclic systems the diazonium ion is of major importance.

Experimental

For general details see *J.*, 1953, 1709. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated.

3β : 17aβ-*Dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*en*-17-*one*.—3β : 17β-Dihydroxy-17α-ethynyl-androst-5-ene was hydrated by Stavely's method (*J. Amer. Chem. Soc.*, 1941, **63**, 3217) to 3β : 17β-dihydroxy-17α-pregn-5-en-20-one, double m. p. 140° and 180°, $[\alpha]_D^{19}$ −61° ± 2° (cf. Shoppee and Prins, *Helv. Chim. Acta*, 1943, **26**, 201), which was rearranged on a column of aluminium oxide in moist benzene to the D-homoketone, m. p. 188°, $[\alpha]_D^{19}$ −108° ± 1° (*c*, 2·12) (Shoppee and Prins, *J.*, 1946, 494, record m. p. 188—190°, $[\alpha]_D^{18}$ −105° ± 5°). The oxime had m. p. 282° (lit., m. p. 283°).

17α-*Amino*-3β : 17aβ-*dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (IX).—The ketoxime (m. p. 282°; 200 mg.) in propanol (20 c.c.; freshly distilled over sodium) was heated with sodium (1 g.) for 2 hr. The cooled solution was neutralised with glacial acetic acid, and solvent removed under reduced pressure; the residue was dissolved in water, the solution made slightly alkaline with 2N-sodium hydroxide, and the precipitated amine collected. This was dissolved in methanol (10 c.c.) and a few drops of concentrated hydrochloric acid were added; the crystalline hydrochloride was filtered off and dissolved in methanol (20 c.c.), and the solution made alkaline with methanolic potassium hydroxide. After partial removal of methanol, water was added dropwise to the hot solution; cooling gave the *amine* (IX) (122 mg.), m. p. 259—261°, $[\alpha]_D^{25}$ −106° ± 4° (*c*, 0·43 in dioxan), after recrystallisation from methanol [Found (after drying at 110°/0·01 mm. for 1 hr.): C, 75·6; H, 10·5; N, 4·6. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6; N, 4·2%].

Deamination of (IX) *to* 3β-*Hydroxy*-17α-*pregn*-5-*en*-20-*one* (VIII).—The amine (95 mg.) was dissolved in 50% acetic acid (2 c.c.), and a solution of sodium nitrite (100 mg.) in 50% acetic acid (2 c.c.) gradually added with stirring; a crystalline precipitate was formed and after 18 hr. the suspension was extracted with ether. Ether-insoluble material (20 mg.) was removed by filtration and the ethereal extract washed with ice-cold sodium hydrogen carbonate solution, ice-cold N-hydrochloric acid, and water, dried, and evaporated. The crystalline residue, m. p. 160—170°, recrystallised from acetone–hexane, gave 3β-hydroxy-17α-pregn-5-en-20-one (35 mg.), m. p. 171—172°, $[\alpha]_D^{18}$ −144° (*c*, 3·3); a mixture with an authentic sample, m. p. 173—174°, prepared by the method of Butenandt and Fleischer (*loc. cit.*) had m. p. 172—174°. The product after sublimation at 140°/0·01 mm. had m. p. 172—173°, $[\alpha]_D^{18}$ −138° ± 2° (*c*, 2·2) (Found: C, 79·05; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·65; H, 10·2%), and was characterised as the acetate, m. p. 171° [Found (after drying at 90°/0·02 mm.): C, 77·3; H, 9·45. Calc. for $C_{23}H_{34}O_3$: C, 77·0; H, 9·55%].

3β : 17aα-*Dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*en*-17-*one*.—3β : 17β-Dihydroxy-17α-ethynyl-androst-5-ene was converted into the diacetate, m. p. 169° (cf. Ruzicka and Hofmann, *Helv. Chim. Acta*, 1937, **20**, 1280), which was hydrated with mercuric oxide–acetic acid–acetic anhydride in presence of boron trifluoride by the procedure of Ruzicka and Meldahl (*ibid.*, 1938, **21**, 1760) to give a 93% yield of 3β : 17β-diacetoxy-17α-pregn-5-en-20-one, m. p. 190°. This ketone (3·3 g.) was rearranged by hot 4% methanolic potassium hydroxide to the D-homoketone (2·6 g.), m. p. 303—305°, which was converted into the oxime, m. p. 280—283°, by treatment in

dioxan under reflux with a filtered solution of hydroxylamine acetate in methanol. The following m. p.s have been recorded: 243—244° (Ruzicka and Meldahl, *Helv. Chim. Acta*, 1938, **21**, 1760), 239° (Ruzicka, Goldberg, and Hunziker, *ibid.*, 1939, **22**, 707), 245—246° (Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 79), 263—265° (Ruzicka and Meldahl, *Helv. Chim. Acta*, 1941, **24**, 1321), 269—272° and 266—274° (Hirschmann and Hirschmann, *J. Biol. Chem.*, 1947, **167**, 7).

17α-*Amino*-3β : 17aα-*dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (VII).—The ketoxime (m. p. 280—283°; 700 mg.) in propanol (80 c.c.; freshly distilled over sodium) was heated with sodium (3 g.) for 2 hr. The cooled solution was neutralised with acetic acid, then evaporated in a vacuum, and water added; the precipitate was filtered off, dried, and crystallised from methanol as plates (155 mg.), m. p. 198—200°. The mother-liquors by concentration and neutralisation with concentrated hydrochloric acid gave the crystalline amine hydrochloride, which was dried and converted into the free base (155 mg.), m. p. 196—198°. After recrystallisation from methanol, the ***amine*** had m. p. 200—201°, $[\alpha]_D^{23}$ −59° ± 2° (*c*, 1·25 in dioxan) [Found (after drying at 110°/0·01 mm. for 4 hr.): C, 75·9; H, 10·8. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6%]. It was unchanged by sodium in boiling propanol during 5 hr. A second preparation gave a product, m. p. 200—201°.

Deamination of (VII) *to* 3β-*Hydroxy*-17α-*pregn*-5-*en*-20-*one* (VIII) *and* 17α : 17aα-*Epoxy*-3β-*hydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (X).—The amine (310 mg.), dissolved in 50% acetic acid (6·5 c.c.), was treated with a solution of sodium nitrite (335 mg.) in 50% acetic acid (6·5 c.c.) and set aside for 18 hr. The product was dissolved in methanol (6 c.c.), to which acetic acid (0·5 c.c.) and Girard's reagent T (465 mg.; freshly washed with methanol and rapidly dried) were added. The mixture was refluxed for 20 min., cooled to 0°, and poured into ice-water (100 c.c.) containing 2N-sodium hydroxide (4·9 c.c.), and at once extracted with ether to yield non-ketonic material (202 mg.). The aqueous solution was made just acid to Congo-red with 2N-hydrochloric acid, kept for 0·5 hr., partially evaporated under reduced pressure to remove methanol, and extracted with ether **to give ketonic material (35 mg.).** Finally the aqueous phase was acidified with 10% of its volume of concentrated hydrochloric acid, kept for 0·5 hr., and again extracted with ether to yield further ketonic material (7 mg.).

The ketonic fraction (42 mg.) was chromatographed on neutralised aluminium oxide (1·4 g.) prepared in pentane; elution with ether–benzene (6 × 8 c.c.; 1 : 8, 1 : 5, and 1 : 3, each twice) gave a solid (15 mg.), which after sublimation at 110°/0·01 mm. and crystallisation from acetone–pentane yielded 3β-hydroxy-17α-pregn-5-en-20-one (VIII) (8 mg.), m. p. 170—172°, $[\alpha]_D^{18}$ −134° ± 3° (*c*, 0·70) [Found (after drying at 80°/0·01 mm. for 4 hr.): C, 79·15; H, 10·35%], mixed m. p. 171—173° with a genuine specimen.

The non-ketonic fraction was chromatographed on neutral aluminium oxide (6 g.) prepared in pentane. Elution with ether–benzene (1 : 3; 4 × 100 c.c.) yielded a crystalline solid (173 mg.), which by recrystallisation from acetone–pentane gave 17α : 17aα-*epoxy*-3β-*hydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (X; R = H), m. p. 196—198°, $[\alpha]_D^{18}$ −114° ± 2° (*c*, 1·40). A good analysis could not be obtained [Found (after drying at 110°/0·01 mm. for 3 hr.): C, 78·7; H, 10·6. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%], which recalls the experience of Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1326) with the saturated analogue (II; R = H). The epoxide showed selective absorption at 208 mμ (ε = 2123) (CR_2·CHR-group), but not in the 290-mμ region (C=O group absent). The *acetate* (X; R = Ac), prepared by using acetic anhydride–pyridine at 18° for 48 hr., after several crystallisations from acetone–pentane formed plates, m. p. 186—187°, $[\alpha]_D^{18}$ −116° ± 1° (*c*, 2·20), which contained 1 mol. of water [Found (after drying at 80°/0·01 mm. for 4 hr.): C, 73·8; H, 9·45. $C_{23}H_{34}O_3,H_2O$ requires C, 73·5; H, 9·6%]; the infra-red spectrum of a Nujol mull exhibited strong bands at 1734 and 1232 cm.$^{-1}$ (acetate group), and bands at 1672, 838, 812, and 800 cm.$^{-1}$ (CR_2·CH group); a weak band at 1305 cm.$^{-1}$ and a strong band at 902 cm.$^{-1}$ are consistent with one epoxide grouping, whilst the hydroxyl band at 3450 cm.$^{-1}$ was too weak to account for more than one hydroxyl group and may have been due to the molecule of water. The epoxide acetate (22 mg.) was hydrogenated with platinum oxide (42 mg.) in acetic acid (2 c.c.) at 20° for 1 hr.; absorption had then ceased; the product was chromatographed on aluminium oxide (1·5 g.) prepared in pentane. Elution with pentane (6-c.c. eluates) gave 11 fractions, of which nos. 2—10 were crystalline and were recrystallised from ether–pentane: fraction 2 (5 mg.), cubes, m. p. 186°, positive tetranitromethane test, consisted of unreduced starting material; fractions 3, 4, and 5 were united (10 mg.) to give needles m. p. 164°; fractions 6 and 7 were united (2 mg.) to give needles, m. p. ~160°; fractions 8, 9, and 10 were united (5 mg.) to give clusters of needles, m. p. 161°; fractions 3—10 gave negative tetranitromethane tests; all the fractions appeared to consist of 3β-acetoxy-17α : 17aα-epoxy-D-homoandrostane (II; R = Ac) [Found (after sublimation of fractions 3, 4,

and 5 at 120—140°/0·02 mm.) : C, 77·1; H, 10·5. Calc. for $C_{23}H_{36}O_3$: C, 76·65; H, 10·1%], for which Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1321) record m. p. 160°.

Similar results were obtained in an independent experiment : the amine (VII) (370 mg.) gave 17-*iso*pregnenolone (VIII) (5 mg.), m. p. 168—172°, $[\alpha]_D^{20}$ −133° ± 5° (*c*, 0·43) and the epoxide acetate (X; R = Ac) (170 mg.), m. p. 183—185° [Found (after drying at 20°/0·05 mm. for 18 hr.) : C, 74·15; H, 9·4%].

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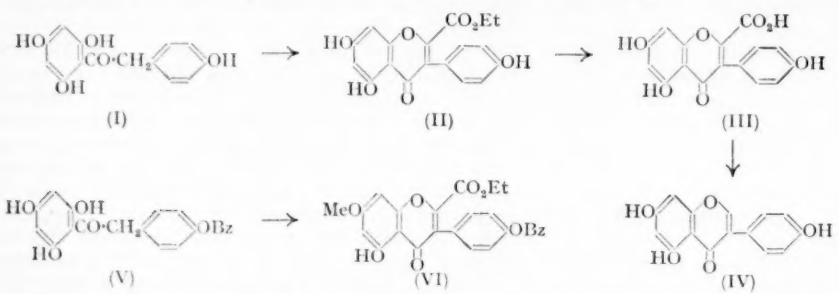
381. *A New Synthesis of* iso*Flavones. Part I.*

By WILSON BAKER, J. CHADDERTON, J. B. HARBORNE, and W. D. OLLIS.

Benzyl *o*-hydroxyphenyl ketones (*e.g.*, I) react at room temperature with ethoxalyl chloride in pyridine to give 2-carbethoxy*iso*flavones (*e.g.*, II) in high yield. Hydrolysis to the carboxylic acids and thermal decarboxylation gives the *iso*flavones (*e.g.*, IV). Unlike the usual ethyl formate–sodium method which can only be satisfactorily used with mono- and di-hydroxylated benzyl phenyl ketones, the new synthesis is satisfactory with the tri- and poly-hydroxylated derivatives, and is particularly suited for the preparation of polyhydroxy- and partly alkoxylated *iso*flavones. Twelve *iso*flavones, six of them naturally occurring, have been synthesised, and the method may be used on a fairly large scale.

The ethoxalylation reaction involves direct *C*-ethoxalylation of the reactive methylene group, and cyclisation to 2-carbethoxy-2-hydroxy*iso*flavanones which have been isolated in some cases.

THE more important methods for the synthesis of *iso*flavones were briefly reviewed in a preliminary communication (Baker, Ollis, *et al.*, *Nature*, 1952, **169**, 706) in which the new process was outlined. The best previous method involved the formylation of benzyl *o*-hydroxyphenyl ketones by ethyl formate and sodium, a method which was first used for preparing chromones unsubstituted in position 2 by Perkin and Robinson in the case of anhydrobrazilic acid (*J.*, 1908, **93**, 504). In early applications (Späth and Lederer, *Ber.*, 1930, **63**, 743; Wesseley, Kornfeld, and Lechner, *Ber.*, 1933, **66**, 685) elevated temperatures were used and the yields of *iso*flavones were poor, but at or below room temperature, improved yields are obtained (Venkataraman, *J.*, 1934, 513, 1120, 1769), and this modification



has been widely used. It proceeds best when all hydroxyl groups in the benzyl phenyl ketone except that involved in cyclisation are protected, and fails when three or more free hydroxyl groups are present (see Baker *et al.*, *loc. cit.*).

The new *iso*flavone synthesis also starts from a benzyl *o*-hydroxyphenyl ketone (*e.g.*, I), but, unlike the ethyl formate process, proceeds equally well (in yields usually between 50 and 80%) when three or even more hydroxyl groups are present. It is particularly suited for the direct preparation of polyhydroxy- and partially alkoxylated hydroxy*iso*flavones. Dealkylation, which is here avoided, is sometimes accompanied by reorientation of a substituent group from position 8 to position 6 in 5-hydroxyflavones, and has been observed in these laboratories also in the *iso*flavone series (R. Winter, Dissertation, Bristol, 1950; I. Dunstan, unpublished observations; see also Baker, Dunstan, Harborne, Ollis, and Winter, *Chem. and Ind.*, 1953, 277; Whalley, *ibid.*, p. 277).

The benzyl *o*-hydroxyphenyl ketone (*e.g.*, I), containing in all *n* free phenolic hydroxyl groups, is treated with $(n + 1)$ equivalents of ethoxalyl chloride, $COCl{\cdot}CO_2Et$, in pyridine at room temperature, and left overnight. Addition of water then gives directly the 2-carbethoxy*iso*flavone (II), from which the related 2-carboxy*iso*flavone (III) is prepared by mild alkaline hydrolysis. The acid (III) is then converted into the *iso*flavone (IV) by decarboxylation at its melting point, a process which is best carried out rapidly with small quantities of acid.

The general applicability of the new method is illustrated by the synthesis of the following *iso*flavones, of which six occur naturally: 7-hydroxy-, 7-hydroxy-3′ : 4′-methylenedioxy- (ψ-baptigenin), 7 : 4′-dihydroxy- (daidzein), 4′-hydroxy-7-methoxy- (formononetin), 5 : 7-dihydroxy-, 5 : 7-dihydroxy-3′ : 4′-methylenedioxy-, 5 : 7 : 4′-trihydroxy- (genistein), 5 : 7-dihydroxy-4′-methoxy- (biochanin-A), 5 : 4′-dihydroxy-7-methoxy- (prunetin), 7 : 4′-dihydroxy-5-methoxy-, 7-hydroxy-4′-nitro-, and 5 : 7-dihydroxy-4′-nitro-*iso*flavone.

The synthesis of prunetin (genistein 7-methyl ether) by the new method involved protection of a phenolic group by benzoylation during and after a Hoesch reaction. Phloroglucinol and *p*-benzoyloxybenzyl cyanide gave 4-benzoyloxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (V), converted by reaction with ethoxalyl chloride in pyridine into 4′-benzoyloxy-2-carbethoxy-5 : 7-dihydroxy*iso*flavone, and thence by partial methylation into 4′-benzoyloxy-2-carbethoxy-5-hydroxy-7-methoxy*iso*flavone (VI). Hydrolysis and decarboxylation then yielded prunetin (5 : 4′-dihydroxy-7-methoxy*iso*flavone).

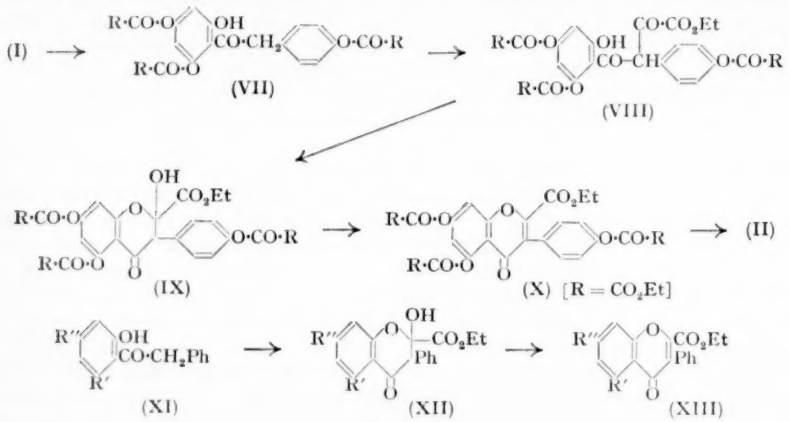
The isomeric 7 : 4′-dihydroxy-5-methoxy*iso*flavone (genistein 5-methyl ether), previously prepared from genistein by dibenzylation followed by methylation and debenzylation (Narasimhachari, Seshadri, and Sethuraman, *J. Sci. Ind. Res. India*, 1951, **10**, *B*, 195; King and Jurd, *J.*, 1952, 3211), has been more directly prepared from *p*-hydroxybenzyl cyanide and phloroglucinol monomethyl ether by the Hoesch reaction. The resulting 2 : 4-dihydroxy-6-methoxyphenyl 4-hydroxybenzyl ketone was then converted into 7 : 4′-dihydroxy-5-methoxy*iso*flavone by the new method [for orientation of ketones prepared by the Hoesch synthesis from phloroglucinol monomethyl ether, see *Org. Reactions*, 1949, **5**, 408, but in this reference for "2 : 6-Dihydroxy-4-methoxybenzophenone" read "2 : 4-Dihydroxy-6-methoxybenzophenone" (Karrer, *Helv. Chim. Acta*, 1919, **2**, 486); other cases not given in *Org. Reactions* are recorded by Sonn and Bülow, *Ber.*, 1925, **58**, 1691, and by Tamura, *Bull. Chem. Soc. Japan*, 1936, **11**, 781]. The ultra-violet absorption spectra of the three monomethyl ethers of genistein are recorded in the Experimental section. In the case of the 5-methyl ether there is a marked shift of the bands towards the shorter wave-lengths.

The usefulness of the new method for larger-scale preparations has been demonstrated by Mr. W. Lawson, of the Courtauld Institute of Biochemistry, Middlesex Hospital, who has synthesised 120 g. of genistein from 2 : 4 : 6-trihydroxyphenyl *p*-methoxybenzyl ketone in a yield of *ca.* 50% (personal communication). The intermediate yields were: ethoxalylation, 50—66%; hydrolysis, almost quantitative; decarboxylation (in portions of 6—8 g., at 300° for 8 min.), demethylation (boiled for 4 hr. with equal volumes of acetic acid and aqueous hydrobromic acid, *d* 1·48), and crystallisation from dilute ethanol, 75%.

Mechanism of the Ethoxalylation Reaction.—Although the conversion of, *e.g.*, *p*-hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (I) into 2-carbethoxy-5 : 7 : 4′-trihydroxy*iso*flavone (II) by reaction with ethoxalyl chloride and pyridine is in practice a single operation, it must involve a number of stages. In the general case these are probably: (1) ethoxalylation of all phenolic hydroxyl groups except one *ortho* to the carbonyl group, giving the

triethoxalyl derivative (VII); (2) direct *C*-ethoxalylation of the reactive methylene group to give (VIII); (3) cyclisation to the 2-carbethoxy-2-hydroxy*iso*flavanone (IX); (4) loss of a molecule of water to give the 2-carbethoxy*iso*flavone (X); (5) removal of the ethoxalyl groups by reaction with dilute acid, giving (II).

The following considerations support and amplify this reaction scheme. (*a*) The fact that it is necessary, in order to obtain the best yields, to employ $(n + 1)$ equivalents of ethoxalyl chloride in the case of a benzyl phenyl ketone containing n phenolic groups, indicates that the first step is the ethoxalylation of all phenolic groups except one in the *ortho* position to the carbonyl group. Phenols are rapidly ethoxalylated under the conditions employed, but a single hydroxyl group *ortho* to a carbonyl group is less readily attacked owing to hydrogen bonding; this is well known both for acylation and for alkylation. (*b*) The *C*-ethoxalylation is regarded as a direct process, rather than acylation of the last hydroxyl group followed by cyclisation to (IX) and dehydration to (X). This alternative is unlikely to occur under the conditions of the reaction. Partial ethoxalylation of the last hydroxyl group probably occurs simultaneously, and, whether or not *C*-ethoxalylation takes place afterwards, this represents a side reaction which does not lead to the 2-carbethoxy*iso*flavone. Preliminary experiments have shown that direct *C*-ethoxalylation of benzyl phenyl ketones occurs with ethoxalyl chloride in pyridine at room temperature, and the resulting 1 : 3-diketones yield co-ordinated copper derivatives. Ethoxalyl chloride, probably in the form of the acyl pyridinium salt, $C_5H_5N{\cdot}CO{\cdot}CO_2Et\}Cl$, reacts differently from simple acid chlorides; *e.g.*, benzyl 2-hydroxy-4 : 6-dimethoxypheny ketone reacts with benzoyl chloride in pyridine to give the *O*-benzoyl derivative (Ollis and Weight, *J.*, 1952, 3826), but the same ketone with ethoxalyl chloride in pyridine gives 2-carbethoxy-5 : 7-dimethoxy*iso*flavone (this paper). (*c*) 2-Carbethoxy-2-hydroxy*iso*flav-



anones have been isolated in several cases. Thus, benzyl *o*-hydroxyphenyl ketone (XI; R′ = R″ = H) and benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) with ethoxalyl chloride under the usual conditions give the non-phenolic 2-carbethoxy-2-hydroxy*iso*flavanones (XII; R′ = R″ = H, and R′ = R″ = OMe respectively). A similar intermediate (XII; R′ = H, R″ = OMe) is also probably formed from benzyl 2-hydroxy-4-methoxyphenyl ketone (XI; R′ = H, R″ = OMe), though in this case it could not be obtained solid and may be a mixture of stereoisomerides. (*d*) These 2-hydroxy*iso*flavanones (XII) are β-hydroxy-carbonyl compounds and readily lose water, *e.g.*, on treatment with hydrochloric acid in acetic acid, to give the 2-carbethoxy*iso*flavones (XIII). With (XII; R′ = R″ = OMe) dehydration is also brought about by potassium hydroxide in pyridine, and simultaneous hydrolysis of the ester group gives the related 2-carboxy*iso*flavone. In many cases of the new synthesis the strongly electron-attracting ethoxalyloxy-groups in positions 5 and 7 of the intermediate 2-hydroxy*iso*flavanones

(as IX) facilitate ionisation of the proton from $C_{(3)}$, in consequence of which spontaneous dehydration occurs with formation of the 2-carbethoxy*iso*flavone (X). It is possible that this elimination of water may occur indirectly *via* an intermediate 2-ethoxalyloxy-derivative; loss of the very stable ethoxalyloxy-ion is likely to occur more readily than loss of the hydroxyl ion (see Southwick and Seivard, *J. Amer. Chem. Soc.*, **1949**, **71**, 2532). (*e*) Ethoxalyl derivatives of phenols are very readily hydrolysed so that pouring the reaction mixture into water, extraction with chloroform, and shaking with dilute hydrochloric acid gives the hydroxylated 2-carbethoxy*iso*flavone (II) or the hydroxylated 2-carbethoxy-2-hydroxy*iso*flavanone, *e.g.*, (XII; R′ = R″ = OH).

Further Observations on the Ethoxalylation Reaction.—Reaction of benzyl *o*-hydroxyphenyl ketones with ethoxalyl chloride and pyridine in boiling benzene gave 2-carbethoxy-*iso*flavones directly in most cases which normally yielded the 2-hydroxy*iso*flavanones, but the yields were very low. However, in the case of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) the product was the *O*-ethoxalyl derivative of (XII; R′ = R″ = OMe), whose structure was proved by hydrolysis with potassium hydroxide in pyridine to (XII; R′ = R″ = OMe), and by boiling with acetic anhydride and sodium acetate which gave the 2-carbethoxy*iso*flavone (XIII; R′ = R″ = OMe).

2-Hydroxy*iso*flavanones have been recognised as intermediates in the ethyl formate *iso*flavone synthesis (Wolfrom, Mahan, Morgan, and Johnson, *J. Amer. Chem. Soc.*, **1941**, **63**, 1248, 1253), and we now find that in the case of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (XI; R′ = R″ = OMe) the primary product of the reaction is 2-hydroxy-5 : 7-dimethoxy*iso*flavanone, which loses water when treated with acetic acid to give 5 : 7-dimethoxy*iso*flavone.

Experimental

Crystallisation was from ethanol, except as given in parentheses. Substances are colourless unless otherwise stated.

*Ethoxalylation of Benzyl 2-Hydroxyphenyl Ketones. 2-Carbethoxyiso**flavones* (with P. J. L. Binns, I. Dunstan, and A. Rutt).—To an ice-cold solution of the benzyl 2-hydroxyphenyl ketone in pyridine (*ca.* 10 c.c. for 1 g. of ketone) was slowly added redistilled ethoxalyl chloride [$(n + 1)$ equivs. for a ketone containing n phenolic groups], with shaking. Next day the mixture was poured into water and extracted with chloroform, and the organic layer washed with 10% hydrochloric acid, dried ($MgSO_4$), and evaporated. The product was then crystallised, and, in some cases, dried over phosphoric anhydride to remove traces of pyridine. The following ten 2-carbethoxy*iso*flavones were prepared in this way.

Benzyl 2 : 4-dihydroxyphenyl ketone (Chapman and Stephen, *J.*, **1923**, **123**, 404; Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2963) gave *2-carbethoxy-7-hydroxyiso**flavone* (31%), plates, m. p. 211·5° (Found: C, 70·3; H, 4·7; OEt, 15·7. $C_{16}H_9O_4{\cdot}OEt$ requires C, 69·7; H, 4·5; OEt, 14·5%) [*monoacetyl* derivative, m. p. 76—77° (Found: C, 67·9; H, 4·2. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%)].

2 : 4-Dihydroxyphenyl 3 : 4-methylenedioxybenzyl ketone (Späth and Schmidt, *Monatsh.*, 1929, **53**, 454) gave 2-carbethoxy-7-hydroxy-3′ : 4′-methylenedioxy*iso*flavone (75%), yellow needles, m. p. 253° (Found: C, 64·5; H, 4·2. $C_{19}H_{14}O_7$ requires C, 64·5; H, 4·0%) [*monoacetyl* derivative, m. p. 170° (Found: C, 63·4; H, 4·0. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·05%)].

2 : 4-Dihydroxyphenyl 4-methoxybenzyl ketone (Baker and Eastwood, *J.*, 1929, 2902) gave *2-carbethoxy-7-hydroxy-4′-methoxyiso**flavone* (76%), m. p. 209—210° (Found: C, 66·6; H, 4·7. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%) [*monoacetyl* derivative, m. p. 123° (Found: C, 65·9; H, 4·8. $C_{21}H_{18}O_7$ requires C, 66·0; H, 4·7%)].

2 : 4-Dihydroxyphenyl 4-hydroxybenzyl ketone (Walz, *Annalen*, 1931, **489**, 118) gave *2-carbethoxy-7 : 4′-dihydroxyiso**flavone* (50%) (from aqueous ethanol), m. p. 194—195° (Found: C, 62·7; H, 4·4. $C_{18}H_{14}O_6{,}H_2O$ requires C, 62·8; H, 4·7%) [*diacetyl* derivative, m. p. 145° (Found: C, 64·1; H, 4·5. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4%)].

2 : 4-Dihydroxyphenyl 4-nitrobenzyl ketone (Joshi and Venkataraman, *J.*, 1934, 513) gave *2-carbethoxy-7-hydroxy-4′-nitroiso**flavone* (40%), m. p. 229° (Found: C, 60·9; H, 3·6; N, 4·0. $C_{18}H_{13}O_7N$ requires C, 60·8; H, 3·7; N, 3·95%) [*monoacetyl* derivative, m. p. 143° (Found: C, 60·0; H, 3·9. $C_{20}H_{15}O_8N$ requires C, 60·5; H, 3·8%)].

3 : 4-*Methylenedioxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone*, prepared by the Hoesch reaction

from phloroglucinol and 3 : 4-methylenedioxyphenylacetonitrile formed needles (65%), m. p. 202° (Found : C, 62·7; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%). It gave *2-carbethoxy-5 : 7-dihydroxy-3′ : 4′-methylenedioxyisoflavone* (87%), yellow needles (from aqueous ethanol), m. p. 223° (Found : C, 61·7; H, 3·7; OEt, 11·2. $C_{17}H_9O_7$·OEt requires C, 61·6; H, 3·8; OEt, 12·2%) [*diacetyl* derivative, m. p. 158—159° (Found : C, 60·6; H, 4·0. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%)].

Benzyl 2 : 4 : 6-trihydroxyphenyl ketone (Badcock *et al., loc. cit.*) gave *2-carbethoxy-5 : 7-dihydroxyisoflavone* (45%), light yellow needles, m. p. 230° (Found : C, 66·1; H, 4·2; OEt, 13·2. $C_{16}H_9O_5$·OEt requires C, 66·25; H, 4·3; OEt, 13·8%) [*diacetyl* derivative, m. p. 153—154° (Found : C, 64·5; H, 4·4. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4%)].

4-Hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (I) (Baker and Robinson, *J.*, 1926, 2716) gave *2-carbethoxy-5 : 7 : 4′-trihydroxyisoflavone* (II) (55%), yellow prisms, m. p. 240—242° (decomp.) (Found : C, 63·0; H, 4·3; OEt, 13·3. $C_{16}H_9O_6$·OEt requires C, 63·15; H, 4·1; OEt, 13·2%) [*triacetyl* derivative, m. p. 181—183° (Found : C, 61·4; H, 4·4; OEt, 10·0. $C_{22}H_{15}O_9$·OEt requires C, 61·5; H, 4·3; OEt, 9·6%)].

4-Methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (Badcock *et al., loc. cit.*) gave *2-carbethoxy-5 : 7-dihydroxy-4′-methoxyisoflavone* (60%), pale yellow needles (from benzene), m. p. 189—190° (Found : C, 64·4; H, 4·6. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%) [*diacetyl* derivative, m. p. 166—167° (Found : C, 62·6; H, 4·7. $C_{23}H_{20}O_9$ requires C, 62·7; H, 4·6%); *dimethyl ether*, m. p. 150—151° (Found : C, 65·6; H, 5·4. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2%)].

4-Nitrobenzyl 2 : 4 : 6-trihydroxyphenyl ketone (Yamashita, *Chem. Abs.*, 1930, **24**, 2443) gave *2-carbethoxy-5 : 7-dihydroxy-4′-nitroisoflavone* (52%), yellow plates (from aqueous ethanol), m. p. 190—191° (Found : C, 58·5; H, 3·8. $C_{18}H_{13}O_8N$ requires C, 58·2; H, 3·5%) [*diacetyl* derivative, m. p. 210—211° (Found : C, 58·0; H, 3·7; N, 3·5. $C_{22}H_{17}O_{10}N$ requires C, 58·0; H, 3·7; N, 3·1%)].

Hydrolysis and Decarboxylation of 2-Carbethoxyisoflavones. Preparation of iso*Flavones* (with P. J. L. Binns, I. Dustan, and A. Rutt).—The preceding esters were hydrolysed by either of the following methods. (*a*) To a solution of the ester in acetone was added 2N-sodium hydroxide (one equiv. for each phenolic group and one for the ester) and then water until the solution became clear. After 24 hr. at room temperature, the acetone was removed, and the solution acidified. (*b*) The ester in acetone or ethanol was warmed for 3—4 hr. with excess of 5% aqueous sodium carbonate. The organic solvent was evaporated, and the cooled solution acidified to pH 4. In each case the solid acid was collected, washed with water, and dried. The *iso*flavone-2-carboxylic acids were obtained as colourless to bright yellow crystalline powders, occasionally containing water of crystallisation. In two cases, the 2-carboxylic acids were purified and analysed (see below), but were usually directly decarboxylated.

In earlier experiments (marked *) decarboxylation was effected by heating the acids *in vacuo* in a sublimation apparatus; the *iso*flavones sublimed. It is, however, better to heat the acids rapidly in portions (*ca.* 50 mg.) some 10° above the m. p.s until evolution of carbon dioxide ceases (2—5 min.). The crude melt was either crystallised from a suitable solvent and washed with aqueous sodium hydrogen carbonate (to remove unchanged acid), or purified through its acetyl derivative.

The following were thus obtained :

7-Hydroxyisoflavone-2-carboxylic acid (80%), needles (from aqueous ethanol), m. p. 247° (decomp.) (Found : C, 64·1; H, 4·2. $C_{16}H_{10}O_5,H_2O$ requires C, 64·0; H, 4·0%). 7-Hydroxy*iso*flavone (75%), prisms, m. p. 213° (Found : C, 75·2; H, 4·3. Calc. for $C_{15}H_{10}O_3$: C, 75·6; H, 4·2%) (Venkataraman, *J.*, 1934, 1120, gives m. p. 215°).

7-Hydroxy-3 : 4-methylenedioxy*iso*flavone-2-carboxylic acid (70%) m. p. 275°. 7-Hydroxy-3′ : 4′-methylenedioxy*iso*flavone (*ψ*-baptigenin) (61%), yellow crystals (from aqueous ethanol), m. p. 292° (Found : C, 67·9; H, 3·7. Calc. for $C_{16}H_{10}O_5$: C, 68·1; H, 3·6%) [monoacetyl derivative, m. p. 165° (Found : C, 66·6; H, 3·7. Calc. for $C_{18}H_{12}O_6$: C, 66·7; H, 3·7%)]. Mahal, Rai, and Venkataraman (*J.*, 1934, 1769) give m. p. 292—293° for *ψ*-baptigenin, and 176° for the monoacetyl derivative.

7-Hydroxy-4′-methoxy*iso*flavone-2-carboxylic acid (98%), m. p. 238°. 7-Hydroxy-4′-methoxy*iso*flavone (formononetin) (91%), plates, m. p. 257° (Found : C, 71·3; H, 4·7. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) [monoacetyl derivative, m. p. 166° (Found : C, 69·3; H, 4·65. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5%)]. Venkataraman (*loc. cit.*) gives m. p. 257° for formononetin, and 170° for the monoacetyl derivative.

7 : 4′-Dihydroxy*iso*flavone-2-carboxylic acid, m. p. 290° (88%). 7 : 4′-Dihydroxy*iso*flavone (daidzein), needles, m. p. 320—328° (decomp.) (98%) (Found : C, 70·6; H, 4·0. Calc. for

$C_{15}H_{10}O_4$: C, 70·9; H, 3·9%) [diacetyl derivative, m. p. 189° (Found: C, 67·8; H, 4·2. Calc. for $C_{19}H_{14}O_6$: C, 67·45; H, 4·1%)]. Venkataraman (*loc. cit.*) gives m. p. 310—322° (decomp.) for daidzein, and 184—187° for the diacetyl derivative.

7-Hydroxy-4′-nitro*iso*flavone-2-carboxylic acid, m. p. 252° (99%). 7-Hydroxy-4′-nitro*iso*flavone, needles, m. p. 292° (98%) (Found: C, 63·2; H, 3·1. $C_{15}H_9O_5N$ requires C, 63·6; H, 3·2%) [*monoacetyl* derivative, m. p. 222—223° (Found: C, 62·7; H, 3·15. $C_{17}H_{11}O_6N$ requires C, 62·8; H, 3·4%)].

5 : 7-Dihydroxy-3′ : 4′-methylenedioxy*iso*flavone-2-carboxylic acid, m. p. 264° (90%). 5 : 7-*Dihydroxy-3′ : 4′-methylenedioxy*iso*flavone*, pale yellow needles (from aqueous ethanol), m. p. 227° (8%*) (Found: C, 64·45; H, 4·4. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%) [*diacetyl* derivative, m. p. 216° (Found: C, 63·4; H, 4·4. $C_{20}H_{14}O_8$ requires C, 62·8; N, 3·7%)].

5 : 7-*Dihydroxy*iso*flavone-2-carboxylic acid*, yellow needles (from aqueous ethanol), m. p. 255° (decomp.) (76%) (Found: C, 62·1; H, 3·7. $C_{16}H_{10}O_6,\frac{1}{2}H_2O$ requires C, 62·5; H, 3·6%). 5 : 7-Dihydroxy*iso*flavone, plates, m. p. 195—196° (from benzene) (25%*) (Found: C, 71·0; H, 4·2. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%) [*diacetyl* derivative, m. p. 173—174° (Found: C, 67·3; H, 4·0. $C_{19}H_{14}O_6$ requires C, 67·45; H, 4·1%)]. Iyer, Shah, and Venkataraman (*Current Sci.*, 1949, **18**, 404; *Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 116) give m. p. 193—194° for 5 : 7-dihydroxy*iso*flavone.

5 : 7 : 4′-Trihydroxy*iso*flavone-2-carboxylic acid (III), m. p. 310° (84%). Acetylation of the crude decarboxylated material gave 5 : 7 : 4′-triacetoxy*iso*flavone (21%), m. p. 195—198° (Walter, *J. Amer. Chem. Soc.*, 1941, **63**, 3273, gives m. p. 200°), hydrolysis of which with aqueous-ethanolic sodium carbonate gave 5 : 7 : 4′-trihydroxy*iso*flavone (genistein) (IV), needles, m. p. 296° (decomp.) (88%) (Found: C, 66·2; H, 3·8. Calc. for $C_{15}H_{10}O_5$: C, 66·7; H, 3·7%). The pure compound gives a green colour with alcoholic ferric chloride. Walter (*loc. cit.*) gives the same m. p., but records a reddish-violet ferric chloride reaction with the natural product.

5 : 7-Dihydroxy-4′-methoxy*iso*flavone-2-carboxylic acid, m. p. 276° (98%). Acetylation of the crude, decarboxylated material gave the diacetyl derivative, needles, m. p. 189—190° (81%) (Found: C, 65·2; H, 4·3. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·4%). Hydrolysis with aqueous-ethanolic sodium carbonate then gave 5 : 7-dihydroxy-4′-methoxy*iso*flavone (biochanin-A) (61%), needles (from aqueous ethanol), m. p. 211—212° (Found: C, 67·1; H, 4·0. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3%). Bose and Siddiqui (*J. Sci. Ind. Res. India*, 1945, **4**, 231) give m. p. 212° for biochanin-A, and 190° for the diacetyl derivative.

5 : 7-Dihydroxy-4′-nitro*iso*flavone-2-carboxylic acid, m. p. 260° (87%). 5 : 7-*Dihydroxy-4′-nitro*iso*flavone*, yellow needles, m. p. 294—295° (23%*) (Found: C, 60·4; H, 3·0; N, 4·8. $C_{15}H_9O_6N$ requires C, 60·2; H, 3·0; N, 4·7%) [*diacetyl* derivative, m. p. 212—213° (Found: C, 59·6; H, 3·2; N, 4·2. $C_{19}H_{13}O_8N$ requires C, 59·5; H, 3·4; N, 3·7%; dimethyl ether, m. p. 220—221° (Iyer, Shah, and Venkataraman, *locc. cit.*, give m. p. 220—222°)].

7 : 4′-*Dihydroxy-5-methoxy*iso*flavone*.—The Hoesch reaction between phloroglucinol monomethyl ether (7·6 g.; Robertson and Subramaniam, *J.*, 1937, 286) and *p*-hydroxybenzyl cyanide (7·3 g.) gave 2 : 4-*dihydroxy-6-methoxyphenyl 4-hydroxybenzyl ketone*, needles (from aqueous ethanol), m. p. 186—188° (8·5 g.) (Found: C, 65·3; H, 5·0; OMe, 10·5. $C_{14}H_{11}O_4$·OMe requires C, 65·7; H, 5·1; OMe, 11·3%). It gives a purple-red ferric chloride reaction. This ketone (2·4 g.) in pyridine (20 c.c.) was treated at 0° with ethoxalyl chloride (3·2 c.c.). After 18 hr. ice was added, and the oil extracted with chloroform (3 × 50 c.c.). When these extracts were washed with 10% aqueous hydrochloric acid, 2-*carbethoxy*-7 : 4′-*dihydroxy-5-methoxy*iso*flavone* separated at the interface. It forms cubes (from aqueous methanol), m. p. 223—224° (0·32 g., 10%) (Found, after drying at 160° for 5 hr.: C, 63·6; H, 4·5. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%). It gave no colour with ferric chloride. This ester was hydrolysed [the acid (83% yield) had m. p. 254—256°] and decarboxylated, giving 7 : 4′-dihydroxy-5-methoxy*iso*flavone (51%), needles (from aqueous ethanol), m. p. 316° (decomp.) (Found, after drying at 160° for 5 hr.: C, 67·7; H, 4·25. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3%). It gave no colour with aqueous-ethanolic ferric chloride. Its diacetyl derivative formed needles (from aqueous ethanol), m. p. 168—170° (88%) (Found: C, 64·8; H, 4·2. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·4%). Narasimhachari, Seshadri, and Sethuraman (*J. Sci. Ind. Res. India*, 1951, **10**, *B*, 195) give m. p. 284—286° for this *iso*flavone; King and Jurd, *J.*, 1952, 3211, give m. p. 302° (decomp.), and 169·5° for the *iso*flavone and its diacetyl derivative.

5 : 4′-*Dihydroxy-7-methoxy*iso*flavone* (*Prunetin*).—*p*-Hydroxybenzyl cyanide (5·0 g.), pyridine (50 c.c.), and benzoyl chloride (5·36 c.c.) gave 4-*benzoyloxybenzyl cyanide* (7·5 g., 84%), needles, m. p. 106—108° (Found: C, 75·6; H, 4·8; N, 6·0. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·6; N, 5·9%). The Hoesch reaction between 4-benzoyloxybenzyl cyanide (8·0 g.) and phloroglucinol

(10 g.) gave 4-*benzoyloxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone* (V) which was washed with hot benzene (500 c.c.) and then crystallised from aqueous ethanol as needles (5·4 g., 44%), m. p. 224° (decomp.) (Found : C, 69·7; H, 4·6. $C_{21}H_{16}O_6$ requires C, 69·2; H, 4·4%). It gave a purple-brown colour with ferric chloride.

The ketone (3 g.) in pyridine (30 c.c.) was treated at 0° with ethoxalyl chloride (4 c.c.) and worked up in the usual way. The 4′-*benzoyloxy*-2-*carbethoxy*-5 : 7-*dihydroxy*isoflavone formed, yellow plates (from methanol) (2·48 g.), m. p. 248° (decomp.) (Found : C, 66·9; H, 3·8. $C_{25}H_{18}O_8$ requires C, 67·3; H, 4·0%). Its *diacetyl* derivative formed plates (from acetone), m. p. 232° (Found : C, 65·7; H, 4·2; OEt, 7·4. $C_{27}H_{17}O_9$·OEt requires C, 65·7; H, 4·2; OEt, 8·4%).

The ester (1·12 g.), benzene (150 c.c.), ignited potassium carbonate (5 g.), and methyl sulphate (0·27 c.c.) were kept at 100° for 2 hr. giving 4′-*benzoyloxy*-2-*carbethoxy*-5-*hydroxy*-7-*methoxy*isoflavone (VI) (0·92 g., 80%), pale yellow plates (from acetone), m. p. 202—204° (Found : C, 67·3; H, 4·1. $C_{26}H_{20}O_8$ requires C, 67·8; H, 4·4%). It gave an intense brown colour with ferric chloride. Hydrolysis gave 5 : 4′-dihydroxy-7-methoxy*iso*flavone-2-carboxylic acid (97%), m. p. 270°, and decarboxylation then gave 5 : 4′-dihydroxy-7-methoxy*iso*flavone (63%), needles (from methanol), m. p. 236° (Found : C, 67·7; H, 4·2; OMe, 11·4. Calc. for $C_{15}H_9O_4$·OMe : C, 67·6; H, 4·3; OMe, 10·9%) [diacetyl derivative, m. p. 218—220° (Found : C, 64·85; H, 4·5. Calc. for $C_{20}H_{16}O_7$: C, 65·2; H, 4·3%)]. King and Jurd (*loc. cit.*) give m. p.s 237—238° and 222·5° for natural prunetin and its diacetyl derivative.

Reaction of Ethoxalyl Chloride with Benzyl o-*Hydroxyphenyl Ketone.* 2-*Carbethoxy*isoflavone. —Ethoxalyl chloride (2·5 c.c.) was added with shaking to benzyl *o*-hydroxyphenyl ketone (2·11 g.; sublimed) in pyridine (20 c.c.). Next day the solution was poured into 10% acetic acid (100 c.c.), and the solid was collected, washed, and dried (3·02 g.), giving 2-*carbethoxy*-2-*hydroxy*isoflavanone, plates (from aqueous ethanol or benzene–light petroleum), m. p. 145° (2·59 g., 83%) (C, 68·8; H, 5·1; OEt, 12·8. $C_{16}H_{11}O_4$·OEt requires C, 69·2; H, 5·1; OEt, 14·4%). The 2 : 4-*dinitrophenylhydrazone*, yellow prisms (from acetic acid), m. p. 206° (decomp.) (Found : C, 58·4; H, 4·25; N, 11·4. $C_{24}H_{20}O_8N_4$ requires C, 58·5; H, 4·1; N, 11·4%). Dehydration of the 2-hydroxy*iso*flavanone by warm acetic and hydrochloric acids during ½ hr. gave 2-carbethoxy*iso*flavone (92%), rectangular plates, m. p. 96—97° (Found : C, 73·6; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

iso*Flavone.*—2-*Carbethoxy*isoflavone (1·0 g.) and concentrated sulphuric acid (10 c.c.) were heated at 100° for ½ hr., then poured into water, and the product crystallised from chloroform–light petroleum (b. p. 60—80°). iso*Flavone*-2-*carboxylic acid* separated as needles (0·5 g., 73%), m. p. 212—213° (Found : C, 71·6; H, 4·3. $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%). Unchanged ester (0·24 g.) was recovered from the mother-liquors.

The acid (0·38 g.) was heated for 15 min. at 220° (till gas evolution ceased), and the product was crystallised from aqueous ethanol, washed with dilute sodium hydrogen carbonate, and dried (0·22 g.; m. p. 128—130°). Crystallisation from light petroleum (b. p. 60—80°) raised the m. p. to 131°, undepressed when mixed with *iso*flavone (m. p. 131°) prepared by the formylation method (Joshi and Venkataraman, *J.*, 1934, 513). The formylation in our hands gave a crude yield of 82% of material, m. p. 126—128°, which, after crystallisation, had m. p. 131° (Joshi and Venkataraman obtained a 40% yield, and m. p. 132°).

Benzyl 2-*Hydroxy*-4-*methoxyphenyl Ketone* (with P. J. L. Binns and R. Winter).—This compound (see Tambor, *Ber.*, 1910, **43**, 1884; Badcock, Cavill, and Whalley, *J.*, 1950, 2963) is best prepared by Bentley and Robinson's method (*J.*, 1950, 1353), but, contrary to a statement in the literature, it can be readily made by the partial methylation of benzyl 2 : 4-dihydroxyphenyl ketone. This ketone (35 g.; m. p. 110—111°, crystallised from benzene), methyl sulphate (17·5 g.), potassium carbonate (100 g.), and benzene (200 c.c.) were boiled for 90 min., cooled, filtered, and evaporated, giving benzyl 2-hydroxy-4-methoxyphenyl ketone (18 g., 51%), needles, m. p. 88°.

Reaction of Ethoxalyl Chloride with Benzyl 2-*Hydroxy*-4-*methoxyphenyl Ketone.*—Ethoxalyl chloride (2 c.c.) was added to benzyl 2-hydroxy-4-methoxyphenyl ketone (2 g.) in pyridine (20 c.c.). Next day the solution was poured into water, extracted with chloroform (3 × 100 c.c.), washed with dilute hydrochloric acid (3 × 100 c.c.), dried, and evaporated, leaving an oil, possibly 2-carbethoxy-2-hydroxy-7-methoxy*iso*flavanone. This was warmed on a steam-bath (½ hr.) with acetic acid (20 c.c.) and concentrated hydrochloric acid (2 c.c.), then added to water, and the solid (2·01 g., 80%) crystallised from ethanol. 2-*Carbethoxy*-7-*methoxy*isoflavone formed prisms, m. p. 130—131° (Found : C, 70·5; H, 4·85. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%). It was also prepared (48%) by methylation of 2-carbethoxy-7-hydroxy*iso*-

flavone, and by reaction of benzyl 2-hydroxy-4-methoxyphenyl ketone with sodium and ethyl oxalate. The crude oil, after being heated with acetic acid and freed from acidic material, gave 2-carbethoxy-7-methoxy*iso*flavone (10%), m. p. and mixed m. p. 130—131° (Found: C, 70·6; H, 4·9%).

7-*Methoxy*iso*flavone* (with R. WINTER).—2-Carbethoxy-7-methoxy*iso*flavone (100 mg.) was dissolved in ethanol (5 c.c.), and 10% aqueous sodium hydroxide (0·14 c.c.) and water (5 c.c.) were added. After 7 hr. the mixture was acidified and diluted, and the solid (89 mg.; m. p. 242°, 97%) collected and crystallised (aqueous ethanol), giving 7-methoxy*iso*flavone-2-carboxylic acid as needles, m. p. 243° (decomp.), alone or when mixed with an authentic specimen (Baker, Pollard, and Robinson, *J.*, 1929, 1473). Decarboxylation at 250° for 10 min. gave 7-methoxyisoflavone (90%), plates (from methanol), m. p. and mixed m. p. 156° (Baker and Robinson, *J.*, 1925, 1986).

Reaction of Benzyl 2-Hydroxy-4 : 6-dimethoxyphenyl Ketone with Ethoxalyl Chloride.—(a) *At room temperature.* Ethoxalyl chloride (3 c.c.) was added with shaking to a solution of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (5 g.) in pyridine (25 c.c.). After 18 hr., water was added, the whole was shaken with chloroform, and the extracts were washed with acid, dried, and evaporated. The 2-*carbethoxy*-2-*hydroxy*-5 : 7-*dimethoxy*iso*flavanone* crystallised from ethanol (35 c.c.) as prisms (4·7 g., 69%), m. p. 148—153° [Found: C, 64·7; H, 5·3; (OEt)(OMe)$_2$, 27·2. $C_{16}H_9O_4(OEt)(OMe)_2$ requires C, 64·6; H, 5·4; (OEt)(OMe)$_2$, 28·8%].

The preceding compound when heated with acetic and hydrochloric acids at 100° for 15 min. gave 2-*carbethoxy*-5 : 7-*dimethoxy*iso*flavone* (85%), m. p. and mixed m. p. with an authentic specimen (see below), 156—158°. When the above hydroxy-flavanone (1 g.) was shaken for 40 min. with potassium hydroxide (0·4 g.), the mixture poured into dilute acid, and the precipitate dissolved in aqueous sodium hydrogen carbonate, filtered and acidified, it gave 5 : 7-*dimethoxy*iso*flavone*-2-*carboxylic acid* (0·6 g., 68%), m. p. 224° (decomp.) (Found: C, 65·8; H, 4·4. $C_{18}H_{14}O_6$ requires C, 66·25; H, 4·3%).

(b) *In boiling benzene.* The ketone (4 g.), benzene (40 c.c.), pyridine (4 c.c.), and ethoxalyl chloride (3·25 c.c.) was kept at 100° for 2½ hr. and then filtered from pyridine hydrochloride, the solution was washed with dilute hydrochloric acid (3 × 25 c.c.), dried, and evaporated, and the oil crystallised from ethanol, giving 2-*carbethoxy*-2-*ethoxalyloxy*-5 : 7-*dimethoxy*iso*flavanone* (2 g., 30%), needles, m. p. 111—112° [Found: C, 60·3; H, 4·6; (OEt)(OMe), 31·6. $C_{18}H_8O_6(OEt)_2(OMe)_2$ requires C, 61·0; H, 5·1; (OEt)(OMe), 32·2%].

A solution of the preceding compound (0·5 g.) in pyridine (3·5 c.c.) and powdered potassium hydroxide (0·3 g.) was shaken for 20 min., and poured into water. The product was crystallised from water, giving 2-carbethoxy-2-hydroxy-5 : 7-dimethoxy*iso*flavanone (0·08 g., 20%), m. p. and mixed m. p. 152° with previous softening. Dehydration with glacial acetic acid gave 2-carbethoxy-5 : 7-dimethoxy*iso*flavone, a compound which was also formed when the above 2-ethoxalyloxy-derivative was heated for 4½ hr. with acetic anhydride and sodium acetate.

5 : 7-*Dimethoxy*iso*flavone* (with D. WEIGHT).—(*a*) A mixture of benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone (3 g.), ethyl formate (40 c.c.), and powdered sodium (3 g.) was stirred at −10° for 2 hr., and kept at 0° for 48 hr. After addition of ice, the mixture yielded to ether a product (1·9 g.) which was crystallised from aqueous ethanol, giving 2-*hydroxy*-5 : 7-*dimethoxy*iso*flavanone*, prisms, m. p. 152° (Found: C, 68·0; H, 5·3. $C_{17}H_{16}O_5$ requires C, 68·05; H, 5·3%). This compound (0·5 g.), when warmed with glacial acetic acid (5 c.c.) for ½ hr. at 100°, gave 5 : 7-dimethoxy*iso*flavone, prisms, m. p. 107° (from ethyl acetate) (Found: C, 72·0; H, 4·9. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%). Iyer, Shah, and Venkataraman (*loc. cit.*) give m. p. 120° for 5 : 7-dimethoxy*iso*flavone.

(*b*) 5 : 7-Dimethoxy*iso*flavone-2-carboxylic acid (0·97 g.) was heated in several portions at 230° for 1—2 min. The product was dissolved in chloroform, washed with dilute, aqueous sodium hydrogen carbonate, dried, and evaporated. The product crystallised from light petroleum (b. p. 100—120°), giving 5 : 7-dimethoxy*iso*flavone, prisms, m. p. 106—108° (0·40 g.).

2-*Carbethoxy*-5 : 7-*dimethoxy*iso*flavone*.—This was prepared (91%) by methylation of 2-carbethoxy-5 : 7-dihydroxy*iso*flavone, and formed pale yellow prisms, m. p. 159—160° (from methanol) [Found: C, 67·8; H, 5·1; (OEt)(OMe)$_2$, 28·8. $C_{16}H_7O_5(OEt)(OMe)_2$ requires C, 67·8; H, 5·1; (OEt)(OMe)$_2$, 30·2%].

o-*Ethoxalyloxy**acetophenone* (with D. WEIGHT).—Ethoxalyl chloride (5 g.) was added to a solution of *o*-hydroxyacetophenone (5 g.) in anhydrous pyridine (10 c.c.) at room temperature. After ½ hr., dilute hydrochloric acid was added, and the oil, after extraction with chloroform, was crystallised from light petroleum (b. p. 40—60°), giving o-*ethoxalyloxyacetophenone* (5·2 g.), needles, m. p. 41° (Found: C, 61·3; H, 4·8. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The

substance underwent hydrolysis on being kept. Basic reagents did not bring about conversion into a β-diketone (Baker–Venkataraman transformation).

Ultra-violet absorption spectra of genistein monomethyl ethers.

Compound	$\lambda_{min.}$ (log ε) (mμ)	$\lambda_{max.}$ (log ε) (mμ)	Inflection (log ε) (mμ)
7-Methyl ether (prunetin)	231 (4·07)	262·5 (4·57)	325 (3·65)
4′-Methyl ether (biochanin-A)	231 (4·10)	262·5 (4·56)	325 (3·71)
5-Methyl ether	227 (4·13)	256 (4·51)	312 (3·81)
[Genistein	231 (4·04)	263 (4·50)	325 (3·71)]

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382. *A New Synthesis of* iso*Flavones. Part II.** 5 : 7 : 2′-*Trihydroxy*iso*flavone.*

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5 : 7 : 2′-Trihydroxy*iso*flavone (I) has been synthesised from 2-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (II; R = Me) by the ethoxalylation process described in the preceding paper. It is not identical with the "*iso*genistein" isolated by Okano and Beppu from soya bean. The intermediate 2-carbethoxy*iso*flavone is converted by hydrobromic acid into 5′ : 7′-dihydroxychromono(2′ : 3′-3 : 4)coumarin (VI) which contains the greater part of the pentacyclic nucleus of rotenone. Evidence is presented which very strongly suggests that the "*iso*genistein," "methylgenistein," and "methyl-*iso*genistein," which Okano and Beppu claim to have isolated from soya bean, are all genistein, and that the same authors' "tatoin," isolated from the same source, is daidzein.

OKANO and BEPPU (*J. Agric. Chem. Soc. Japan*, 1939, **15**, 645) isolated from soya bean a glycoside, which when hydrolysed gave a pale yellow, phenolic substance, $C_{15}H_{10}O_5$, m. p. 302°, giving a triacetate, m. p. 189°, and a dimethyl ether, m. p. 120—125°. This aglycone was stated to be 5 : 7 : 2′-trihydroxy*iso*flavone (I), because alkaline hydrolysis gave phloroglucinol, formic acid, *o*-hydroxyphenylacetic acid, and 2-hydroxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (II; R = H). Because of its supposed structural similarity to genistein (5 : 7 : 4′-trihydroxy*iso*flavone) it was named "*iso*genistein."

We have now synthesised 5 : 7 : 2′-trihydroxy*iso*flavone (I), and find that it is colourless, and is dimorphic, having m. p.s 187° and 222—223°; the higher-melting form is the more stable. The triacetyl derivative has m. p. 132—134°, and the dimethyl ether has m. p. 160°. It is thus very different from "*iso*genistein," a conclusion which we reported earlier (*Chem. and Ind.*, 1952, 1058) and which has independently been reached by Dr. S. Varadarajan and Professor T. R. Seshadri (personal communication, 28th November, 1952), by Karmarkar, Shah, and Venkataraman (*Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 552), and by Dr. W. B. Whalley (personal communication, 2nd February, 1953).

The preparation of (I) was achieved by means of the new synthesis described in Part I. The benzyl phenyl ketone (II; R = H) could not be obtained from phloroglucinol and 2-hydroxybenzyl cyanide by the Hoesch reaction, probably because the cyanide formed a non-reactive cyclic imine hydrochloride (III) in presence of hydrogen chloride. 2-Methoxybenzyl cyanide was therefore condensed with phloroglucinol by the Hoesch reaction, giving 2-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (II; R = Me), and this was then treated with ethoxalyl chloride in pyridine to give 2-carbethoxy-5 : 7-dihydroxy-2′-methoxy*iso*flavone (IV). Alkaline hydrolysis and decarboxylation then yielded 5 : 7-dihydroxy-2′-methoxy*iso*flavone (V), and final demethylation of (V) gave 5 : 7 : 2′-trihydroxy*iso*flavone (I). Monomethylation of (V) gave 5-hydroxy-7 : 2′-dimethoxy*iso*flavone.

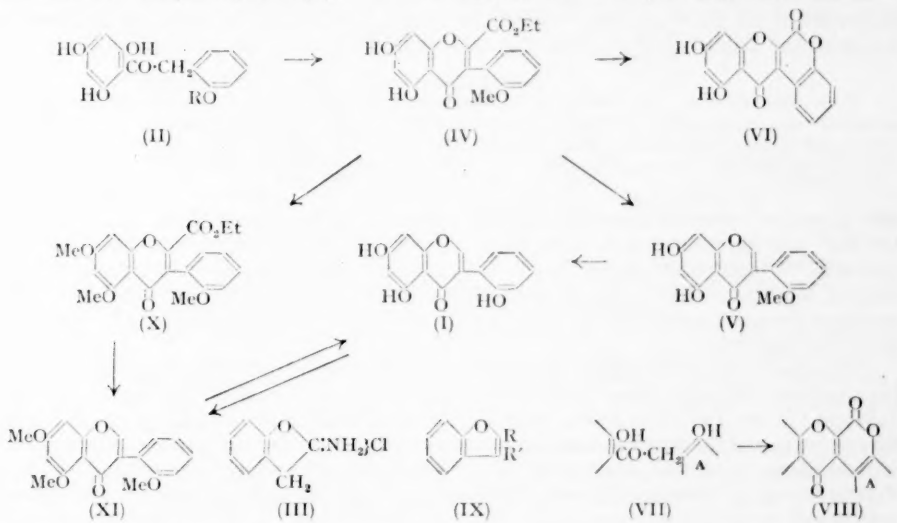
The action of hydrobromic acid–acetic acid upon 2-carbethoxy-5 : 7-dihydroxy-2′-methoxy*iso*flavone (IV) caused hydrolysis of the ester group, demethylation, and lactonis-

* Part I, preceding paper.

ation, giving the bright yellow lactone (VI) of 2-carboxy-5 : 7 : 2′-trihydroxy*iso*flavone [5′ : 7′-dihydroxychromono(2′ : 3′-3 : 4)coumarin]. This substance is of interest in connection with the problem of the synthesis of compounds of the rotenone type, as it contains four of the five fused rings found in rotenonone, the non-degraded oxidation product of rotenone (Butenandt, *Annalen*, 1928, **464**, 257).

After our work was completed we found that a partial synthesis involving ethoxalylation, and formation of an *iso*flavone nucleus and a chromono(2′ : 3′-3 : 4)coumarin had been previously carried out. La Forge (*J. Amer. Chem. Soc.*, 1932, **54**, 3377) treated deritol, partial formula (VII), with ethoxalyl chloride in pyridine at room temperature for 48 hours, and obtained rotenonone, partial formula (VIII). In the light of the present work this unexpected result clearly involved *C*-ethoxalylation, cyclisation to the 2-carbethoxy-*iso*flavone derivative, and interaction of the ester group with the phenolic group of nucleus A.

The demethylation of 5 : 7-dihydroxy-2′-methoxy*iso*flavone (V) was effected by hydrobromic acid in acetic acid and by aluminium chloride in benzene. The latter was used in order to avoid the possibility of hydrolysis of the heterocyclic ring and subsequent closure to give a benzofuran, either 3-(2 : 4 : 6-trihydroxybenzoyl)benzofuran (IX; R = H, R′ = 2 : 4 : 6-trihydroxybenzoyl), or 3-formyl-2-(2 : 4 : 6-trihydroxyphenyl)benzofuran



(IX; R = 2 : 4 : 6-trihydroxyphenyl, R′ = CHO). Such a change occurs when 2′-methoxyflavones are demethylated with hydrogen iodide (Philbin and Wheeler, *Chem. and Ind.*, 1952, 449), and Dr. R. Winter (Dissertation, Bristol, 1950) has found that 5 : 7 : 8-trihydroxy-2-methyl*iso*flavone is converted into 5 : 6 : 7-trihydroxy-2-methyl*iso*flavone by prolonged treatment with hydrobromic acid. In view of the difference between our final product and the " *iso*genistein " described by Okano and Beppu, it was desirable to obtain additional proof that no fundamental change had occurred during demethylation. Hence the intermediate compound 2-carbethoxy-5 : 7-dihydroxy-2′-methoxy*iso*flavone (IV) was methylated to 2-carbethoxy-5 : 7 : 2′-trimethoxy*iso*flavone (X), then hydrolysed and decarboxylated to 5 : 7 : 2′-trimethoxy*iso*flavone (XI), and this substance was identical with the trimethyl ether of 5 : 7 : 2′-trihydroxy*iso*flavone (I), thus confirming the structure of the latter. A further proof of the *iso*flavone structure of (I) is that the ultra-violet absorption spectra curves of genistein and of (I) are almost identical (see Experimental section). Partial demethylation of 5 : 7 : 2′-trimethoxy*iso*flavone (XI) with hydrobromic acid gave 5 : 2′-dihydroxy-7-methoxy*iso*flavone.

5 : 7 : 2′-Trihydroxy*iso*flavone is œstrogenic, and is active in mice at a dose of 4 mg.;

it therefore possesses about one-quarter of the activity of the isomeric 5 : 7 : 4′-trihydroxy-*iso*flavone (genistein) (Bradbury and White, *J.*, 1951, 3447). We are indebted to Dr. R. B. Bradbury of the Commonwealth Scientific and Industrial Research Organisation and Dr. D. H. Curnow of the University of Western Australia for these tests.

We suggest that the name " *iso*genistein " of the material, m. p. 302°, isolated by Okano and Beppu from soya bean should lapse, and as there are many possible isomers of genistein there is no adequate reason for transferring it to 5 : 7 : 2′-trihydroxy*iso*flavone.

The iso*Flavones of Soya Bean.*—Soya beans have been proved to contain genistein and daidzein (7 : 4′-dihydroxy*iso*flavone) (Walz, *Annalen*, 1931, **489**, 118), and in addition Okano and Beppu (*loc. cit.*) claim to have isolated 5 : 7 : 2′-trihydroxy*iso*flavone (" *iso*genistein "), and 5 : 7 : 4′- (" methylgenistein ") and 5 : 7 : 2′-trihydroxy-8-methyl*iso*flavone (" methyl*iso*genistein "). The present paper shows that " *iso*genistein " is not (I), and, although Shriner and Hull (*J. Org. Chem.*, 1945, **10**, 228) claim to have synthesized " methylgenistein " the work of W. B. Whalley (paper presented at the 122nd Meeting of the American Chemical Society, September 14—19, 1952) has shown that these two *C*-methyl*iso*flavones are not identical with the materials isolated by Okano and Beppu from soya bean.

It has now been observed that there is a strong resemblance between the physical properties of the three products isolated by Okano and Beppu and those of genistein as shown in the Table. Indeed, with the exception of the curiously high melting point of

	M. p.	Triacetyl derivative	Dimethyl ether	Trimethyl ether	Glycoside
Genistein	300°	195—198°	140—142°	162—163°	256°
" Methylgenistein "	298	184	125—134	154—155	—
" Methyl*iso*genistein "	301—302	188	242 (142 ?)	152—153	255
" *iso*Genistein "	302	189	120—125	—	265

242° given for " methyl*iso*genistein dimethyl ether " which appears likely to be an error for 142°, the agreement is so remarkable as to render it almost certain that " methylgenistein," " methyl*iso*genistein," and " *iso*genistein " were all genistein of slightly varying degrees of purity. This seems the more likely, because some of the supposed hydrolysis products were not satisfactorily characterised and the elementary analyses are consistent with this suggestion.

A further product " tatoin," supposed to be 5 : 4′-dihydroxy-8-methyl*iso*flavone, has been isolated from soya bean by Okano and Beppu (*loc. cit.*), and by Bhandari, Bose, and Siddiqui (*J. Soc. Ind. Res., India*, 1949, **8B**, 217). The structure has not yet been proved by synthesis, and the annexed comparison suggests that " tatoin " may prove to be identical with daidzein (7 : 4′-dihydroxy*iso*flavone). The recorded analyses of " tatoin " and its derivatives agree equally well with the formulæ $C_{15}H_{10}O_4$ and $C_{16}H_{12}O_4$ for the parent compound.

	M. p.	Diacetyl derivative, m. p.	Monomethyl ether, m. p.	Dimethyl ether, m. p.
" Tatoin " [a]	318°	185°	160—163° [e]	165
" [b]	316—317	185	—	—
Daidzein	315—320 [c]	182 [c]	7- 218—220 [d]	153 [c]
			4′- 255—257 [d]	

[a] Okano and Beppu (*loc. cit.*). [b] Bhandari, Bose, and Siddiqui (*loc. cit.*). [c] Walz (*loc. cit.*). [d] Agkoramurthy, Narasimhachari, and Seshadri (*Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 257). [e] Tatoin monomethyl ether, prepared by monomethylation of " tatoin," with diazomethane, is likely to be a mixture, and a mixture of the two monomethyl ethers of daidzein might well melt as low as 160—163°.

Experimental

Analyses are by Mr. B. S. Noyes, Bristol.

2-*Methoxybenzyl Cyanide.*—This was prepared from *o*-methoxybenzaldehyde *via* the azlactone by Bergel, Haworth, Morrison, and Rinderknecht (*J.*, 1944, 263), but the method was only very briefly described, and only the azlactone intermediate was characterised.

o-Methoxybenzaldehyde (80 g.), hippuric acid (120 g.), anhydrous sodium acetate (40 g.), and acetic anhydride (220 c.c.) were heated on a steam-bath for ½ hr. and cooled. Alcohol

(50 c.c.) was added and the azlactone collected, and washed with alcohol and then with hot water (yield, 124 g., 75%). The azlactone (50 g.) was boiled for 1 hr. with sodium hydroxide (25 g.) in water (150 c.c.), and the cooled solution diluted with water (150 c.c.) and saturated with sulphur dioxide. The filtered solution, now free from benzoic acid, was heated for 1 hr. on a steam-bath in an open basin with concentrated hydrochloric acid (75 c.c.), and cooled. o-*Methoxyphenylpyruvic acid* was collected (17 g., 50%), and crystallised from benzene in rhombic plates, m. p. 157° (Found: C, 62·5; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·8; H, 5·2%). It gave a red solution in concentrated sulphuric acid. The crude acid (15 g.) was added to a warm solution of hydroxylamine hydrochloride (12 g.) in 8% aqueous sodium hydroxide, the mixture acidified after 24 hr., and the *oxime* (15 g., 92%) collected. It separated from ethyl acetate in prisms, m. p. 157° with evolution of carbon dioxide (Found: N, 6·9. $C_{10}H_{11}O_4N$ requires N, 6·7%). The oxime (20 g.) was warmed with acetic anhydride (20 c.c.) until evolution of carbon dioxide ceased (20 min.), then poured into water, and the 2-methoxybenzyl cyanide (14 g., 98%) crystallised from methanol, giving rhombic plates, m. p. 69·5° (Found: C, 73·1; H, 6·3; N, 9·8. Calc. for C_9H_9ON: C, 73·5; H, 6·2; N, 9·5%).

2-*Methoxybenzyl* 2 : 4 : 6-*Trihydroxyphenyl Ketone* (II; R = Me).—A solution of 2-methoxybenzyl cyanide (5·1 g.) and phloroglucinol (10 g.) in dry ether (150 c.c.) was saturated with hydrogen chloride at 0° in presence of powdered zinc chloride (0·5 g.) and kept at 0° for 6 days. After addition of dry ether, the liquid layer was decanted, and the solid ketimine hydrolysed with water (500 c.c.) (steam-bath, 2 hr.). 2-*Methoxybenzyl* 2 : 4 : 6-*trihydroxyphenyl ketone* separated from aqueous ethanol as needles (7·1 g., 74%), m. p. 167—169° (Found: C, 65·9; H, 5·1; OMe, 11·5. $C_{14}H_{11}O_4$·OMe requires C, 65·7; H, 5·1; OMe, 11·3%). Its alcoholic solution gave a purple colour with a trace of ferric chloride.

2-*Carbethoxy*-5 : 7-*dihydroxy*-2′-*methoxy*iso*flavone* (IV)—Ethoxalyl chloride (60 c.c.) was added at 0° with shaking to a solution of 2-methoxybenzyl 2 : 4 : 6-trihydroxyphenyl ketone (37 g.) in pyridine (250 c.c.), and after 24 hr. the mixture was poured into water and extracted with chloroform (3 × 500 c.c.), and the organic layer washed with dilute hydrochloric acid (4 × 200 c.c.), dried ($MgSO_4$), and evaporated. The solid was crystallised from aqueous methanol, giving 2-*carbethoxy*-5 : 7-*dihydroxy*-2′-*methoxy*iso*flavone* as deep yellow needles (40 g., 84%), m. p. 154—156° (Found: C, 63·9; H, 4·6. $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%). It gave an intense red-brown ferric chloride colour. The *diacetyl* derivative separated from ethanol in colourless prisms, m. p. 139—140° [Found: C, 62·7; H, 4·8; (OMe) (OEt), 17·7. $C_{20}H_{12}O_7$(OMe)(OEt) requires C, 62·7; H, 4·6; (OMe)(OEt), 17·3%].

5 : 7-*Dihydroxy*-2′-*methoxy*iso*flavone* (V).—The preceding ester (40 g.) in acetone (400 c.c.) was heated at 100° for 4 hr. with 5% aqueous sodium carbonate (400 c.c.). Evaporation of the solvent and acidification gave 5 : 7-dihydroxy-2′-methoxy*iso*flavone-2-carboxylic acid, which, after drying at 110°, formed a yellow powder (32 g., 87%), giving a reddish-brown ferric chloride reaction.

This acid (370 mg.) was decarboxylated in small portions at *ca.* 290° for 2—3 min., and the crude melt crystallised from aqueous ethanol, giving 5 : 7-*dihydroxy*-2′-*methoxy*iso*flavone* (V) as colourless needles (250 mg., 78%), m. p. 195—197° (Found: C, 67·3; H, 4·0. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3%). Alternatively the acid (1·5 g.) was decarboxylated and directly acetylated, giving 5 : 7-*diacetoxy*-2′-*methoxy*iso*flavone*, which crystallised from methanol as needles (0·90 g., 53%), m. p. 192—193° (Found: C, 65·3; H, 3·9; OMe, 8·1. $C_{19}H_{13}O_6$·OMe requires C, 65·2; H, 4·4; OMe, 8·4%).

5 : 7 : 2′-*Trihydroxy*iso*flavone* (I).—(*a*) The *iso*flavone (V) (200 mg.) was heated (3 hr.) at 140—150° with hydrobromic acid (2·3 c.c.; *d* 1·5) and acetic acid (2·3 c.c.), giving, after dilution, 5 : 7 : 2′-*trihydroxy*iso*flavone* (I). This separated from aqueous ethanol as colourless, fibrous needles (52 mg., 27%), m. p. 187° (Found: C, 66·5; H, 4·2. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). This *iso*flavone is dimorphic, and when crystallised later from the same solvent or from benzene, was obtained as clusters of prismatic needles, m. p. 222—223°. A mixture of the two forms sintered at *ca.* 187°, but melted at 222—223°. Its alcoholic solution gives a purple-brown ferric chloride reaction. The *triacetyl* derivative separates from aqueous methanol as colourless needles, m. p. 132—134° (Found: C, 63·5; H, 4·0. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%).

(*b*) 5 : 7-Diacetoxy-2′-methoxy*iso*flavone (150 mg.), acetic acid (2·5 c.c.), and hydrobromic acid (2·5 c.c.) were heated at 140° for 2·5 hr. giving the *iso*flavone (I) (52 mg., 47%).

(*c*) The *iso*flavone (V) (200 mg.) in dry benzene (40 c.c.) and powdered aluminium chloride (1 g.) were boiled for 4 hr. The benzene was evaporated, the aluminium complex decomposed with hydrochloric acid at 0°, and the product crystallised from aqueous ethanol and then

from chloroform–light petroleum, giving a solid (156 mg., 82%), m. p. 185—186° alone or mixed with a specimen prepared by method (*a*).

*5-Hydroxy-7 : 2′-dimethoxy*iso*flavone*.—The *iso*flavone (V) (80 mg.), dry benzene (10 c.c.), potassium carbonate (1 g.), acetone (5 c.c.), and methyl sulphate (0·03 c.c.) were kept at 100° for 2 hr. After filtration, the solvents were evaporated, leaving the solid *5-hydroxy-7 : 2′-dimethoxy*iso*flavone*; this separated from ethanol as needles (72 mg., 86%), m. p. 160° [Found : C, 68·6; H, 5·2; OMe, 20·1. $C_{15}H_8O_3(OMe)_2$ requires C, 68·4; H, 4·7; OMe, 20·8%].

*5 : 7 : 2′-Trimethoxy*iso*flavone* (XI).—(*a*) 2-Carbethoxy-5 : 7-dihydroxy-2′-methoxy*iso*flavone (IV) (14·4 g.), methyl sulphate (10 c.c.), and potassium carbonate (10 g.) in acetone (144 c.c.) were heated on a steam-bath for 18 hr., more potassium carbonate and methyl sulphate (10 c.c.) being added after 3 hr. Addition of water gave *2-carbethoxy-5 : 7 : 2′-trimethoxy*iso*flavone* (X) which separated from ethanol as a microcrystalline powder, m. p. 142—144° [Found : C, 65·8; H, 5·0; (OEt)(OMe)$_3$, 36·3. $C_{16}H_6O_3(OEt)(OMe)_3$ requires C, 65·6; H, 5·2; (OEt)(OMe)$_3$, 35·9%].

The preceding crude ester (*ca.* 15 g.) was heated on a steam-bath for 3 hr. with 5% aqueous sodium carbonate (100 c.c.) and ethanol (100 c.c.). The ethanol was removed by distillation, and acidification then gave the related carboxylic acid (10 g., 70% yield from IV) as a white powder. The acid was decarboxylated at *ca.* 260° for 10 min., and the product crystallised from aqueous ethanol (charcoal), washed with aqueous sodium hydrogen carbonate (yield 6·8 g., 77%; m. p. 130—134°), and crystallised from light petroleum (b. p. 100—120°), giving *5 : 7 : 2′-trimethoxy*iso*flavone* (XI) as colourless needles, m. p. 138—139° [Found : C, 69·45; H, 5·0; OMe, 27·3. $C_{15}H_7O_2(OMe)_3$ requires C, 69·2; H, 5·1; OMe, 29·8%].

(*b*) 5 : 7 : 2′-Trihydroxy*iso*flavone (I) (116 mg.), acetone (20 c.c.), methyl sulphate (1 c.c.), and potassium carbonate (1 g.) were boiled for 20 hr., giving finally 5 : 7 : 2′-trimethoxy*iso*flavone, m. p. 138—139°, in 68% yield.

5′ : 7′-Dihydroxychromono(2′ : 3′-3 : 4)coumarin (VI).—2-Carbethoxy-5 : 7-dihydroxy-2′-methoxy*iso*flavone (IV) (300 mg.), acetic acid (5 c.c.), and hydrobromic acid (5 c.c.; *d* 1·5) were heated at 140° for 2 hr. and poured into water. The solid (225 mg., 90%) crystallised from pyridine, giving *5′ : 7′-dihydroxychromono(2′ : 3′-3 : 4)coumarin* (VI) as orange-yellow plates which deepened in colour at *ca.* 300°, but did not melt below 360° (Found : C, 65·3; H, 2·9. $C_{16}H_8O_6$ requires C, 64·9; H, 2·7%). It was insoluble in aqueous sodium hydrogen carbonate, and its alcoholic solution gave a brown colour with ferric chloride. The *dibenzoyl* derivative separated from acetone as colourless plates (93%), m. p. 248° (Found : C, 71·3; H, 3·1. $C_{30}H_{16}O_8$ requires C, 71·4; H, 3·2%).

*5 : 2′-Dihydroxy-7-methoxy*iso*flavone*.—5 : 7 : 2′-Trimethoxy*iso*flavone (XI) (3 g.), hydrobromic acid (30 c.c.; *d* 1·5), and acetic acid (30 c.c.) were boiled for 6 hr. and poured into water. The dark, resinous precipitate was chromatographed on alumina in acetone, and the eluate yielded a crystalline product which separated from ethanol as colourless plates (132 mg.), m. p. 175—177° (Found : C, 67·6; H, 3·6. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3%). *5 : 2′-Dihydroxy-7-methoxy*iso*flavone* gives a purple ferric chloride reaction. The *diacetyl* derivative separates from aqueous ethanol in needles, m. p. 108—110° (Found : C, 65·7; H, 4·2. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%).

Demethylation of the trimethyl ether (XI) (2 g.) with hydriodic acid (15 c.c.; *d* 1·7) and acetic anhydride (10 c.c.) for 1 hr. at 150° gave a mixture of partially demethylated products (1·52 g.), m. p. 164—170°. Some of this material (0·6 g.) was demethylated further with aluminium chloride in benzene, and gave 5 : 7 : 2′-trihydroxy*iso*flavone (0·4 g.), m. p. 184—186° (cf. Whalley, *loc. cit.*).

Ultra-violet absorption characteristics.

Compound	$\lambda_{min.}$ (log ε) (mμ)	$\lambda_{max.}$ (log ε) (mμ)	Inflections (log ε) (mμ)
5 : 7 : 4′-Trihydroxy*iso*flavone (genistein) ...	231 (4·04)	263 (4·50)	325 (3·71)
5 : 7 : 2′-Trihydroxy*iso*flavone	234 (4·17)	261 (4·43)	325 (3·78)
5 : 2′-Dihydroxy-7-methoxy*iso*flavone	234 (4·18)	259 (4·45)	282 (4·08)
			320 (3·68)

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383. *N-Ethyl(or -Methyl or -Phenyl)-N-2-halogenoethyl-1′(or -2′)-naphthylmethylamines. Part I. Structure and Pharmacological Activity.*

By N. B. Chapman and J. W. James.

A series of *N*-alkyl(or aryl)-*N*-2-halogenoethyl-1′(or 2′)-naphthylmethylamines, 1- or 2-$C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$, has been prepared by the action of phosphorus pentachloride, tribromide, or tri-iodide suspended in chloroform on the corresponding alcohols, or, where X = F, by the action of 1-bromo-2-fluoroethane on the secondary amines. They inhibit the action of adrenaline and of histamine more or less save when R = Ph or X = F. The relevance of these observations to the mode of pharmacological action of the compounds is discussed.

Reports by Loew and Micetich (*J. Pharmacol.*, 1948, **94,** 339; 1949, **95,** 448) and by Nickerson and Gump (*ibid.*, 1949, **97,** 25) that certain *N*-substituted 2-halogenoethylamines (*e.g.*, I, II; R = Et, X = Cl) inhibited the action of histamine and of adrenaline led us to undertake a systematic study, utilising all the halogens, of certain of these compounds in which one of the substituents is a 1(or 2)-naphthylmethyl group. We had already made some progress with the synthesis of another type of histamine antagonist also derived from naphthalene (Chapman, James, and Williams, *J.*, 1952, 4024).

(I) $1\text{-}C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$ $\qquad$ $2\text{-}C_{10}H_7 \cdot CH_2 \cdot NR \cdot CH_2 \cdot CH_2X$ (II)

Our object was threefold: first, to examine the dependence of pharmacological activity on mobility of the halogens by systematic variation of the halogen, including fluoro-compounds in which the fluorine could be confidently predicted to be immobile; secondly, to examine the hypothesis advanced by Nickerson and Gump (*loc. cit.*), that the pharmacologically active species is a substituted ethyleneiminium ion, by varying the structure so as to inhibit loss of halogen, and by studying the kinetics of the cyclisation where it did occur. The kinetic work will be reported later. Cyclisation was inhibited by a phenyl substituent which so reduced electron availability at the nitrogen atom that the compounds were stable in solution in aqueous acetone even at elevated temperatures. Finally, we wished to examine the influence of the structure of the carbon skeleton on pharmacological activity, and the claim that this type of compound irreversibly inhibited the action of histamine. We have worked in collaboration with J. D. P. Graham and G. P. Lewis, Department of Pharmacology, Welsh National School of Medicine, Cardiff.

At the inception of this investigation no chemical details of the compounds examined pharmacologically had been published. Since then reports of some of the compounds we have synthesised have appeared (Rieveschl and Coleman, U.S.P. 2,573,605; cf. Gump and Nikowitz, *J. Amer. Chem. Soc.*, 1950, **72,** 1309; Kerwin and Ulyott and their collaborators, *ibid.*, 1951, **73,** 4162, 5682; Geissman, Hochman, and Fukuto, *ibid.*, 1952, **74,** 3313). Preliminary accounts of our own work have been given (Chapman, James, Graham, and Lewis, *Chem. and Ind.*, 1951, 633; 1952, 805). Geissman *et al.* (*loc. cit.*) have overlooked this in claiming priority for their synthesis of *N*-ethyl-*N*-2-iodoethyl-1′-naphthylmethylamine hydriodide.

Condensing 1-naphthylmethyl chloride or 2-naphthylmethyl bromide (Chapman and Williams, *J.*, 1952, 5044) with 2-anilino-, 2-ethylamino-, or 2-methylamino-ethanol gave the alcohols corresponding to the required halogeno-compounds. The alcohols were converted into chlorides by the action of phosphorus pentachloride in dry chloroform, into bromides by using phosphorus tribromide similarly, and into iodides by using phosphorus tri-iodide. The iodide (I; R = Ph) was obtained by Finkelstein's reaction (*Ber.*, 1910, **43,** 1528) from the bromo-compound (cf. Geissman *et al.*, *loc. cit.*). The compounds were usually obtained as hydrogen halide salts. Synthesis of the fluoro-compounds proved more difficult. Condensation of 1-naphthylmethyl chloride or 2-naphthylmethyl bromide with an excess of anhydrous ethylamine or methylamine gave *N*-ethyl(or methyl)-1- or -2-naphthylmethylamines. By utilising the difference in reactivity between CH_2F

and CH_2Br, these secondary amines could be converted into the required fluorine-containing tertiary amines by condensation with 0·5 mol. of 1-bromo-2-fluoroethane in boiling ethyl methyl ketone. Only one of these (namely, I; R = Me, X = F) readily gave crystalline salts.

The pharmacological properties of these compounds are fully described by Graham and Lewis (*Brit. J. Pharmacol.*, 1953, **18**, 54). When R = Ph, or when R = Me or Et and X = F, the compounds (I and II) do not inhibit the action of adrenaline, and antihistamine activity is very small. Mobility of the halogen is clearly a necessary condition for pharmacological activity. The same condition is, of course, also necessary but not sufficient for cyclisation to an ethyleneiminium ion. Moreover, variation of halogen is as important as other structural changes in influencing activity (for details see Graham and Lewis, *loc. cit.*).

Evidence relating to the formation, structure and stability, and pharmacological rôle of ethyleneiminium ions derived from these halogeno-amines will be discussed later.

Experimental

Preparation of Intermediates.—1-Naphthylmethyl chloride was prepared by the method given in " Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. 1, p. 70, and 2-naphthylmethyl bromide by Chapman and Williams' method (*J.*, 1952, 5044). 2-Anilinoethanol was prepared by Dashen and Brewster's method (*Trans. Kansas Acad. Sci.*, 1937, **40**, 103), *viz.*, interaction of aniline and 40% (w/v) aqueous ethylene chlorohydrin at 100° for 6 hr. 2-Ethyl- and 2-methyl-aminoethanol were prepared by Knorr and Schmidt's and Knorr and Matthes' methods respectively (*Ber.*, 1898, **31**, 1072, 1069). 1-Bromo-2-fluoroethane was prepared by Saunders, Stacey, and Wilding's method (*J.*, 1949, 773) or by Hoffmann's method (*J. Org. Chem.*, 1950, **15**, 430).

2-(N-1′-*Naphthylmethyl*-N-*phenylamino*)*ethanol* (I; R = Ph, X = OH).—1-Naphthylmethyl chloride (26 g., 0·15 mole) was added with stirring to a mixture of 2-anilinoethanol (26 g., 0·19 mole), water (50 c.c.), and sodium hydrogen carbonate (16 g., 0·19 mole). After the initial reaction had subsided the mixture was heated at 100° (4 hr.) and, after cooling, ethanol was added until the mixture was homogeneous. On further cooling the crude substituted aminoethanol separated and was filtered off. On exposure to air it rapidly became green, but could be decolorised chromatographically on alumina. The crude material, m. p. 77—85°, is adequate for subsequent syntheses.

2-(N-1′-*Naphthylmethyl*-N-*phenylamino*)*ethanol picrate* (from ethanol) had m. p. 128·5—129·5° (Found: C, 59·0; H, 4·6; N, 11·3. $C_{25}H_{22}O_8N_4$ requires C, 59·3; H, 4·4; N, 11·1%).

N-2-*Halogenoethyl*-N-*phenyl*-1′-*naphthylmethylamines* (I; R = Ph, X = Cl, Br, or I).—Adding, during 1 hr., a solution, which had been decolorised chromatographically, of *N*-1′-naphthylmethyl-*N*-phenyl-2-aminoethanol (13·6 g., 0·05 mole) in dry (K_2CO_3) chloroform (50 c.c.) to a stirred suspension of phosphorus pentachloride (10·3 g., 0·05 mole) in dry chloroform at 0°, followed by boiling for 2—3 hr. gave, after distillation of chloroform and phosphoryl chloride at 15 mm., N-2-*chloroethyl*-N-*phenyl*-1′-*naphthylmethylamine*, a green oil, which on crystallisation from ethanol had m. p. 103·5—104° (yield 50%) (Found: C, 76·7; H, 6·05; N, 4·9; Cl, 12·0. $C_{19}H_{18}NCl$ requires C, 77·1; H, 6·1; N, 4·75; Cl 12·0%).

N-2-*Bromoethyl*-N-*phenyl*-1′-*naphthylmethylamine* (crystallised from ethanol or acetone) was prepared similarly in 65% yield (a 50% excess of phosphorus tribromide was used), had m. p. 128° (Found: C, 67·2; H, 5·5; N, 3·9; Br, 23·3. $C_{19}H_{18}NBr$ requires C, 67·0; H, 5·3; N, 4·1; Br, 23·5%). This compound was converted (96% yield) into N-2-*iodoethyl*-N-*phenyl*-1′-*naphthylmethylamine* [crystallised from acetone or light petroleum (b. p. 60—80°)], m. p. 152·5—153°, by heating it with sodium iodide in acetone (cf. Finkelstein, *Ber.*, 1910, **43**, 1528) (Found: C, 58·9; H, 4·8; N, 3·7; I, 32·9. $C_{19}H_{18}NI$ requires C, 58·9; H, 4·7; N, 3·6; I, 32·8%).

2-[N-*Ethyl*(*or Methyl*)-N-1′-*naphthylmethylamino*]*ethanol* (cf. B.P. 641,454).—Stirring 2-ethylaminoethanol (60 g., 0·67 mole), water (150 c.c.), 1-naphthylmethyl chloride (120 g., 0·67 mole), and potassium carbonate (100 g., 0·85 mole) at 100° for 8 hr. gave, after acidification, extraction of neutral material with ether, and basification, a 72% yield of 2-(*N*-ethyl-*N*-1′-naphthylmethylamino)ethanol, b. p. 122°/0·001 mm. (lit., 187°/5 mm.), n_D^{20} 1·5900 [*picrate*, m. p. 103·5—104° (Found: C, 54·7; H, 4·9; N, 12·6. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%)]. *N*-2-(Methyl-*N*-1′-naphthylmethylamino)ethanol, b. p. 125°/0·004 mm. (lit., 172°/5 mm.), was similarly prepared (61%) [*picrate*, m. p. 96° (Found: C, 53·8; H, 4·4; N, 12·4. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5; N, 12·6%)].

N-*Ethyl*(*or Methyl*)-1′-*naphthylmethylamine*.—1-Naphthylmethyl chloride (30 g., 0·17 mole) was added dropwise to anhydrous ethylamine (50 g., 0·90 mole) at its b. p., under a reflux condenser cooled to −10°, after which the mixture was kept at room temperature for 12 hr. when ethylamine hydrochloride separated. The product was acidified with dilute hydrochloric acid, any insoluble material being extracted with ether. The oily base was then liberated with aqueous sodium hydroxide, extracted with ether, and dried (Na_2SO_4), the ether removed, and the N-*ethyl*-1-*naphthylmethylamine* (65%) distilled; it had b. p. 88°/0·0007 mm., n_D^{20} 1·6180 [*hydrochloride*, m. p. 171° (Found: C, 69·4; H, 7·2; N, 6·4; Cl, 16·2. $C_{13}H_{15}N$,HCl requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%); *hydrobromide*, m. p. 143° (Found: Br, 29·4. $C_{13}H_{15}N$,HBr requires Br, 30·0%)].

N-*Methyl*-1-*naphthylmethylamine*, prepared similarly (69%), had b. p. 90°/0·03 mm., n_D^{20} 1·6180 [*hydrochloride*, m. p. 185° (Found: C, 69·6; H, 6·85; N, 6·7; Cl, 16·9. $C_{12}H_{13}N$,HCl requires C, 69·4; H, 6·8; N, 6·7; Cl, 17·1%)].

N-*Ethyl*(*or Methyl*)-N-2-*halogenoethyl*-1′-*naphthylmethylamines* (I; R = Et or Me; X = F, Cl, Br, or I).—*N*-Ethyl-*N*-1′-naphthyl-2-aminoethanol (21·8 g., 0·095 mole) in dry chloroform was added dropwise to phosphorus pentachloride (20·8 g., 0·1 mole) suspended in dry chloroform, and the mixture boiled until no more hydrogen chloride was evolved. Chloroform and phosphoryl chloride were distilled off at 15 mm., and the product crystallised from dry ethanol (yield 95%).

N-2-Chloroethyl-*N*-ethyl-1′-naphthylmethylamine hydrochloride had m. p. 166·5—167° (lit., 171°) (Found: C, 63·2; H, 6·8; N, 4·9; Cl, 24·9. Calc. for $C_{15}H_{18}NCl$,HCl: C, 63·4; H, 6·7; N, 4·9; Cl, 24·9%).

N-2-Chloroethyl-*N*-methyl-1′-naphthylmethylamine hydrochloride, prepared similarly (100%), had m. p. 187° (lit., 198°) (Found: C, 61·8; H, 6·5; N, 5·5; Cl, 25·9. Calc. for $C_{14}H_{16}NCl$,HCl: C, 62·2; H, 6·3; N, 5·2, Cl, 26·2%).

N-2-Bromoethyl-*N*-ethyl-1′-naphthylmethylamine hydrobromide was similarly prepared, by using phosphorus tribromide (0·15 mol.) [Rieveschl and Coleman (*loc. cit.*) heated the corresponding substituted aminoethanol with 40% aqueous hydrobromic acid to obtain the same product], m. p. 167° (lit., 167°) (yield 94%) (Found: C, 47·9; H, 5·3; N, 3·9; Br, 42·5. Calc. for $C_{15}H_{18}NBr$,HBr: C, 48·3; H, 5·1; N, 3·75; Br, 42·8%).

N-2-*Bromoethyl*-N-*methyl*-1′-*naphthylmethylamine hydrobromide*, similarly prepared (63%), had m. p. 191° (Found: C, 46·9; H, 4·8; N, 4·1; Br, 44·0. $C_{14}H_{16}NBr$,HBr requires C, 46·8; H, 4·8; N, 3·9; Br, 44·5%).

N-*Ethyl*-N-2-*iodoethyl*-1′-*naphthylmethylamine hydriodide* was similarly prepared by using phosphorus tri-iodide, the product being precipitated from ethanol with dry (sodium) ether and slowly recrystallised from dry ethanol (yield 56%); it had m. p. 165·5—166° (Found: C, 38·5; H, 4·2; N, 3·2; I, 54·3. $C_{15}H_{18}NI$,HI requires C, 38·6; H, 4·1; N, 3·0; I, 54·4%). A mixture of red phosphorus and iodine was found unsuitable for this preparation.

N-2-*Iodoethyl*-N-*methyl*-1′-*naphthylmethylamine hydriodide*, prepared similarly (49%), had m. p. 147·5 (Found: C, 36·7; H, 3·7; N, 2·9; I, 56·4. $C_{14}H_{16}NI$,HI requires C, 37·1; H, 3·8; N, 3·1; I, 56·0%).

N-*Ethyl*(*or Methyl*)-N-2-*fluoroethyl*-1′-*naphthylmethylamine*.—1-Bromo-2-fluoroethane (14·1 g., 0·11 mole) and *N*-ethyl-1-naphthylmethylamine (42 g., 0·22 mole) were heated under reflux in ethanol at the b. p. (63 hr.), the ethanol distilled at 15 mm., and the residue made alkaline with sodium hydroxide. The resultant oil was extracted with ether and, after drying (Na_2SO_4) and removal of ether, the mixture was acetylated by boiling acetic anhydride and a trace of sulphuric acid (4 hr.). The product was poured into ice-water, the insoluble material extracted with ether, the residue made alkaline, the oil extracted with ether and dried (Na_2SO_4), and the ether removed.

N-*Ethyl*-N-2-*fluoroethyl*-1′-*naphthylmethylamine* was then distilled (b. p. 116—120°/0·0018 mm.; yield, 6 g., 25% based on 1-bromo-2-fluoroethane) (Found: C, 77·4; H, 7·9; N, 6·2. $C_{15}H_{18}NF$ requires C, 77·9; H, 7·8; N, 6·8%). This base does not readily form crystalline salts with mineral acids or the stronger organic acids and only with difficulty forms a picrate, m. p. 144·5°.

N-Methyl-1-naphthylmethylamine (15 g., 0·08 mole) was boiled under reflux with 1-bromo-2-fluoroethane (14 g., 0·11 mole) and sodium hydrogen carbonate (9·3 g., 0·11 mol.) in ethyl methyl ketone (50 c.c.) for 35 min. The hot reaction mixture was filtered, and excess of 1-bromo-2-fluoroethane and solvent were removed at 15 mm.

N-2-*Fluoroethyl*-N-*methyl*-1′-*naphthylmethylamine* was then distilled (b. p. 99—102°/0·001 mm.; n_D^{20} 1·5840; yield 75%) (Found: C, 77·5; H, 8·1; N, 6·7. $C_{14}H_{16}NF$ requires C, 77·4;

H, 7·4; N, 6·45%). The *hydrochloride* (from dry ethanol), m. p. 143° (Found: C, 66·4; H, 7·2; N, 5·55; Cl, 14·0. $C_{14}H_{16}NF,HCl$ requires C, 66·3; H, 6·8; N, 5·5; Cl, 14·0%), was obtained by the action of dry hydrogen chloride on the base dissolved in benzene.

2-[N-*Ethyl*(*or Methyl*)-N-2′-*naphthylmethylamino*]*ethanol* (II; R = Et or Me, X = OH).—2-Naphthylmethyl bromide (125 g., 0·57 mole) was condensed with 2-ethylaminoethanol (50 g., 0·56 mole) as for the α-isomer, to give 2-(N-*ethyl*-N-2′-*naphthylmethylamino*)*ethanol* (69%), b. p. 138°/0·007 mm., n_D^{18} 1·5896 (Found: N, 5·85. $C_{15}H_{19}ON$ requires N, 6·1%). 2-(N-*Methyl*-N-2′-*naphthylmethylamino*)*ethanol*, b. p. 120°/0·003 mm., n_D^{20} 1·6014, was similarly prepared (62%) (Found: N, 6·5. $C_{14}H_{17}ON$ requires N, 6·5%).

N-*Ethyl*(*or Methyl*)-2-*naphthylmethylamine*.—Condensing ethylamine or methylamine with 2-naphthylmethyl bromide dissolved in an equal weight of benzene, but otherwise as in the preparation of the α-isomers, gave *N*-ethyl-2-naphthylmethylamine (50%), b. p. 89—92°/0·002 mm., n_D^{18} 1·6099 [*hydrochloride*, m. p. 230° (Found: C, 70·6; H, 7·4; N, 6·0; Cl, 15·95%)], and *N*-methyl-2-naphthylmethylamine (40%), b. p. 90°/0·02 mm., n_D^{14} 1·6168 [*hydrochloride*, m. p. 227° (Found: C, 69·4; H, 6·85; N, 6·7; Cl, 16·9%)], respectively. If pure solid 2-naphthylmethyl bromide was condensed with anhydrous ethylamine, a mixture of the above secondary amine with the corresponding tertiary amine was produced.

N-*Ethyl*(*or Methyl*)-N-2-*halogenoethyl*-2′-*naphthylmethylamines* (II; R = Et or Me, X = F, Cl, Br, or I).—The following were prepared as for the α-isomers, except where stated. N-2-*Chloroethyl*-N-*ethyl*-2′-*naphthylmethylamine hydrochloride*, m. p. 191·5° (78%) (Found: C, 63·6; H, 6·8; N, 4·8; Cl, 24·8%). N-2-*Chloroethyl*-N-*methyl*-2′-*naphthylmethylamine hydrochloride*, m. p. 176·5° (80%) (Found: C, 61·8; H, 6·5; N, 5·3; Cl, 26·2%). N-2-*Bromoethyl*-N-*ethyl*-2′-*naphthylmethylamine hydrobromide*, m. p. 196·5° (67%) (Found: C, 48·6; H, 5·4; N, 3·7; Br, 43·6%). N-2-*Bromoethyl*-N-*methyl*-2′-*naphthylmethylamine hydrobromide*, m. p. 183·5° (72%) (Found: C, 47·1; H, 5·3; N, 4·05; Br, 43·9%). N-*Ethyl*-N-2-*iodoethyl*-2′-*naphthylmethylamine hydriodide*, m. p. 179° (54%) Found: C, 38·8; H, 4·2; N, 3·1; I, 54·6%). N-2-*Iodoethyl*-N-*methyl*-2′-*naphthylmethylamine hydriodide*, m. p. 189° (55%) (Found: C, 37·2; H, 3·7; N, 3·2; I, 56·2%).

Experiments with Mr. J. F. A. Williams, B.Sc.—N-*Ethyl*(*or Methyl*)-N-2-*fluoroethyl*-2′-*naphthylmethylamine*. *N*-Ethyl-2-naphthylmethylamine (25 g., 0·13 mole) and 1-bromo-2-fluoroethane (8·6 g., 0·067 mole) in ethyl methyl ketone (30 c.c.) were boiled for 4 hr. The mixture was filtered and cooled, dry ether (100 c.c.) was added, and the product again filtered. The solvents were removed, the residue was dissolved in 6N-hydrochloric acid, and insoluble material extracted with methylene dichloride. The residue was made alkaline with sodium hydroxide, the oil formed extracted with ether and dried (Na_2SO_4), the ether removed, and the residue distilled, giving N-*ethyl*-N-2-*fluoroethyl*-2′-*naphthylmethylamine*, b. p. 112°/0·004 mm., n_D^{22} 1·5680 (yield, 52%) (Found: C, 78·3; H, 7·80; N, 6·35%).

N-2-*Fluoroethyl*-N-*methyl*-2′-*naphthylmethylamine*, b. p. 115°/0·04 mm., n_D^{20} 1·5772 (yield, 52%) (Found: C, 76·6; H, 7·25; N, 6·25%), was prepared similarly.

N-1-Naphthylmethylaniline was prepared as an intermediate for a synthesis which proved unsuccessful, as follows. Aniline (372 g., 4 moles), 1-naphthylmethyl chloride (176·5 g., 1·0 mole), and water (100 c.c.) were heated with stirring at 100° for 8 hr. The cooled mixture was filtered, and the oily layer separated and washed with aqueous sodium chloride solution. After drying (Na_2SO_4), the aniline was removed at 15 mm., and N-1-*naphthylmethylaniline* (220 g., 94%) was distilled and crystallised from ethanol; it had m. p. 64°, b. p. 162—164°/0·003 mm. (Found: C, 87·5; H, 6·7; N, 6·0. $C_{17}H_{15}N$ requires C, 87·5; H, 6·5; N, 6·0%).

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The University, Southampton. [*Received, January 30th*, 1953.]

384. *The Liquid Dinitrogen Tetroxide Solvent System. Part XIII.* Factors related to the Mechanism of Metal–Dinitrogen Tetroxide Reactions; the Dipolar Nature of Dinitrogen Tetroxide in the Liquid State.*

By C. C. Addison and J. Lewis.

The paper considers factors having a direct bearing on the reaction mechanisms which occur in metal–liquid dinitrogen tetroxide reactions. The following two factors concern the ion-pair mechanism: (*a*) Apparently discordant evidence on the dipole moments of the N_2O_4 and NO_2 molecules has been correlated. Recalculations based on published data show that all experimental results may be interpreted satisfactorily if it is assumed that $\mu_{N_2O_4}$ is zero, and that μ_{NO_2} varies with temperature, although no simple explanation of this unique variation in μ_{NO_2} is available. (*b*) A mechanism for the formation of $[NO^+][NO_3^-]$ ion-pairs in the liquid is postulated which involves initial heterolytic dissociation into $[NO_2^+][NO_2^-]$, followed immediately by the oxidative transfer of an oxygen atom. The following factors support the mechanism involving direct metal–tetroxide reactions: (*c*) The products of reaction of sodium and zinc with gaseous N_2O_4–NO_2 mixtures at temperatures below 150° have been shown to be identical with those obtained from the liquid tetroxide. (*d*) Conditions are defined under which sodium nitrite is stable in contact with gaseous N_2O_4–NO_2 mixtures.

In previous papers in this series (*e.g.*, Part VIII, *J.*, 1951, 2833; Part IX, *J.*, 1951, 2838) kinetic measurements of the reaction between metallic zinc and liquid dinitrogen tetroxide have been interpreted on the basis of two mechanisms of reaction: the first, operative at low temperatures, involves an electron-transfer reaction between the zinc and ion-pairs of the form $[NO^+][NO_3^-]$, and the second, which predominates above 14°, involves fission of the N–N bond of the tetroxide on impact at the metal surface, followed by reaction between the metal and nitrogen dioxide. The metal oxide produced is then assumed to react directly with dinitrogen tetroxide to give the metal nitrate. Since reactions involving other metals (notably uranium) may be interpreted on the same mechanisms, it is necessary to consider the evidence upon which these reaction mechanisms are based.

There are five factors of importance to which reference has not been made previously. They concern (*a*) the dipole moments of the N_2O_4 and NO_2 molecules, (*b*) the mode of formation of $[NO^+][NO_3^-]$ ion-pairs, (*c*) the reaction of metals with gaseous dinitrogen tetroxide, (*d*) the stability of nitrites in the gaseous tetroxide, and (*e*) the reaction of metal oxides with liquid and gaseous dinitrogen tetroxide. The first four factors are discussed in this paper, and the fifth in the following paper.

(a) *Dipole Moments of* N_2O_4 *and* NO_2 *Molecules.*—The existence of ion-pairs $[NO^+][NO_3^-]$ in small concentration in liquid dinitrogen tetroxide was postulated in Part IV (*J.*, 1951, 1294) on the assumption that the N_2O_4 molecule in the liquid state has a zero dipole moment. However, since various authors give conflicting interpretations of their experimental data, it is necessary to assess the evidence in support of this zero value.

The first determination of the dipole moment of nitrogen dioxide was made by Ghosh and Mohanti (*Z. Physik*, 1929, **30**, 531) who found $\mu_{NO_2} = 0{\cdot}62$ D for the gas. These calculations are of limited accuracy, since they were based on Nernst-bridge measurements of the dielectric constant ε by Badeker (*Z. physikal. Chem.*, 1901, **36**, 316). A later determination by Zahn (*Z. Physik*, 1933, **34**, 461) gave the values $\mu_{NO_2} = 0{\cdot}39$ D and $\mu_{N_2O_4} = 0{\cdot}55$ D; this work was criticised on grounds of interpretation by Williams, Schwingle, and Winnings (*J. Amer. Chem. Soc.*, 1934, **56**, 1427; 1936, **58**, 200) who deduced a zero value for $\mu_{N_2O_4}$, and a value of μ_{NO_2} which varied with temperature. Zahn (*Z. Physik*, 1935, **36**, 461) later agreed with this interpretation. However, independent measurements by

* Part XII, *J.*, 1952, 1399.

Schulz (*ibid.*, 1938, **109**, 517) led to the values $\mu_{NO_2} = 0{\cdot}32$ D and $\mu_{N_2O_4} = 0{\cdot}42$ D; Schulz implied that the criticism of Zahn's interpretation by Williams *et al.* was incorrect. The assumption of a zero dipole for the N_2O_4 molecule therefore necessitates a temperature-variable dipole moment for the NO_2 molecule, whereas if μ_{NO_2} is assumed to be constant, a finite value for $\mu_{N_2O_4}$ results which is greater than that of μ_{NO_2}.

Zahn and Schulz assume that the contribution of N_2O_4 and NO_2 molecules to the total electrical polarisation is determined by the relative amounts present (f_1 and f_2, respectively). Hence,

$$P = f_1(A_1 + B_1/T) + f_2(A_2 + B_2/T)$$

where A_1 and A_2 are the optical constants given by

$$A = \frac{M}{\rho}\left(\frac{n^2 - 1}{n^2 + 2}\right) = \frac{4}{3}\pi N\alpha_0$$

where N is Avogadro's number and α is the polarisability of the molecule. Assuming B_1 and B_2 to be constant ($B = 4\pi N\mu^2/9k$, where k is Boltzmann's constant), these authors determined values for $\mu_{N_2O_4}$ and μ_{NO_2}, but did not obtain sufficient data to enable a value for the dipole moment of each molecule to be calculated at any one temperature. If μ_{NO_2} varies with temperature, then Debye's equation cannot be applied. In order to compare the two sets of experimental data, the results of Williams *et al.* at two temperatures have been substituted in the above equation, and the values of $\mu_{N_2O_4}$ and μ_{NO_2} are given in Table 1.

TABLE 1.

	(*a*) $T_1 = 298°$ K, $T_2 = 318°$ K.					(*b*) $T_1 = 298°$ K, $T_2 = 343°$ K.				
$\mu_{N_2O_4}$	0·283	0·332	0·284	0·287	0·238	0·283	0·361	0·389	0·267	0·457
μ_{NO_2}	0·423	0·422	0·410	0·415	0·457	0·387	0·387	0·373	0·395	0·359
	(*c*) $T_1 = 318°$ K, $T_2 = 343°$ K.					(*d*) $T_1 = 298°$ K, $T_2 = 368°$ K.				
$\mu_{N_2O_4}$	0·469	0·348	0·360	0·321	0·391	0·333	0·391	0·306	0·393	0·471
μ_{NO_2}	0·352	0·389	0·370	0·387	0·382	0·341	0·341	0·342	0·337	0·339

The greater spread of results in the case of $\mu_{N_2O_4}$ no doubt arises from the smaller concentration of N_2O_4 molecules at the higher temperature, leading to greater errors in its evaluation. The means of the results in Table 1 are compared in Table 2 with Schulz's

TABLE 2.

		(*a*)	(*b*)	(*c*)	(*d*)
$\mu_{N_2O_4}$	Schulz's results	0·416	0·416	0·415	0·411
	Calc. from data of Williams *et al.*	0·28	0·38	0·39	0·39
μ_{NO_2}	Schulz's results	0·321	0·320	0·320	0·321
	Calc. from data of Williams *et al.*	0·42	0·38	0·38	0·34

results (*loc. cit.*). If it is assumed that $\mu_{N_2O_4} = 0$, Schulz's data may be recalculated to give μ_{NO_2} at a series of temperatures (see Figure). Schulz applied an arbitrary correction of 5% for the contribution of atom polarisation, but this correction has been excluded from the results shown in the Figure. In view of the agreement shown, it is clear that the different conclusions of the above authors arise solely from differences in interpretation.

The values for the dielectric constant and refractive index of liquid dinitrogen tetroxide have been substituted into Onsager's equation (*J. Amer. Chem. Soc.*, 1936, **58**, 1486), *viz.*,

$$\frac{(\varepsilon - n^2)(2\varepsilon + n^2)}{\varepsilon(n^2 + 2)^2} \cdot \frac{M}{\rho} = \frac{4\pi N\mu^2}{9kT}$$

In comparison with the above values, this equation gives $\mu = 0{\cdot}51$ D for dinitrogen tetroxide in the liquid state. In view of the limited applicability of this equation in media of low dielectric constant, the value obtained is reasonably close to that determined by Schulz. If the dipolar character of liquid dinitrogen tetroxide arises from a finite dipole in the tetroxide molecule, the agreement between the two independent $\mu_{N_2O_4}$ values would provide evidence that the N_2O_4 structure is the same in the gas as in the liquid state. However, this assumption is not justified (see below), and the above agreement is fortuitous.

None of the results discussed above leads to a definite conclusion regarding the value for $\mu_{N_2O_4}$, but appropriate evidence is available from the measurements of ε made by Williams *et al.* (*loc. cit.*) on gaseous NO_2–N_2O_4 mixtures, at a single temperature, in which the NO_2/N_2O_4 ratio was varied by change in pressure. Since no temperature change is involved, all dipole moments are constant, and the Debye equation may be applied directly to the experimental results. When this is done, a zero dipole moment for the N_2O_4 molecule is obtained.

This conclusion involves a temperature-variable dipole for the NO_2 molecule. Williams *et al.* (*loc. cit.*) have shown that this variation is larger than can be accounted for on the assumption that the molecule possesses two moments corresponding to two vibrational states. From ultra-violet absorption measurements, Harris and King (*J. Chem. Phys.*, 1940, **8**, 775) considered the possibility of nitrogen dioxide's possessing two low-lying electronic states of approximately the same energy. We have examined the variation in μ_{NO_2} from this point of view. When one activated state only is considered, we have

$$\mu^2 = \left[\frac{\mu_0^2 + K\mu_1^2 e^{-h\nu/kT}}{1 + Ke^{-h\nu/kT}}\right]$$

Since the observed moment μ decreases with increasing temperature, the moment μ_1 in the excited state must be less than the moment μ_0 in the ground state. On the assumption that the statistical weight factor K is unity, the difference between the values of μ/μ_0 at 300° K and 400° K has been calculated for a range of values of μ_1/μ_0 and $h\nu/kT$ (Table 3).

□ *Calc. from results of Schulz* (loc. cit.).
○ *Calc. from results of Zahn* (loc. cit.).
× *Results of Williams* et al. (loc. cit.).

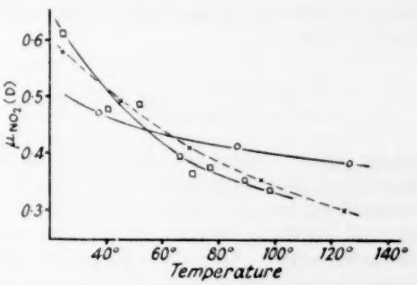


TABLE 3.

		300° K		400° K		
μ_1/μ_0		$h\nu/kT$	μ/μ_0	$h\nu/kT$	μ/μ_0	$(\mu/\mu_0)_{300} - (\mu/\mu_0)_{400}$
0·5	{	3·3	0·9911	2·5	0·9809	0·0102
		1·0	0·9304	0·75	0·9164	0·0140
		0·33	0·8892	0·25	0·8838	0·0054
0·1	{	3·3	0·9839	2·5	0·9651	0·0188
		1·0	0·8708	0·75	0·8433	0·0274
		0·33	0·7897	0·25	0·7784	0·0113
0·0	{	3·3	0·9820	2·5	0·9614	0·0206
		1·0	0·8851	0·75	0·8241	0·0310
		0·33	0·7624	0·25	0·7497	0·0230

The value of μ_0 is not known. However,

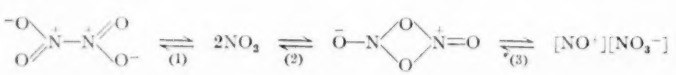
$$\mu_0 = (\mu_{300} - \mu_{400})/[(\mu/\mu_0)_{300} - (\mu/\mu_0)_{400}]$$

and from the Figure, $\mu_{300} - \mu_{400}$ is approximately 0·3 D; the maximum value of the denominator (col. 6, Table 3) then gives a value of about 10 D for μ_0. In order that the calculated value of μ_0 should be in a range of possible values, a degeneracy of the molecule in the activated state has been considered. Maximum variation in dipole moment with temperature occurs when $h\nu = kT$ (Van Vleck, *Phys. Reviews*, 1927, **29**, 729; **30**, 31) and also as μ_1/μ_0 approaches zero. The statistical weight K being assigned values of **1**, **2**, **3**, and **4** (and on the assumption that $\mu_1/\mu_0 = 0$ and $h\nu = kT$ at 300° K), the differences

between the two values of μ/μ_0 are 0·031, 0·042, 0·046, and 0·048, respectively. Variation of K within reasonable limits does not therefore bring about the necessary decrease in μ_0, and it is not possible to explain the temperature variation in μ_{NO_2} by assuming one excited state; the assumption of three electronic levels involves too many unknown parameters to permit corresponding calculations to be made. However, the considerable amount of evidence for the symmetrical structure of the N_2O_4 molecule in the solid and in the gaseous state supports the assumption of a zero value for $\mu_{N_2O_4}$ (and thus a temperature-variable μ_{NO_2}) in the liquid state also.

(b) *Mode of Formation of* $[NO^+][NO_3^-]$ *Ion-pairs.*—Of the various possible ion-pairs, the $[NO^+][NO_3^-]$ pair has been postulated, since almost all the chemical reactions of the N_2O_4 molecule are in accord with this formulation. In the absence of any plausible mechanism involving either intermolecular or intramolecular rearrangements of the N_2O_4 molecules themselves, atom transfer may be considered to occur subsequent to the initial homolytic (i) or heterolytic (ii) dissociation of N_2O_4 molecules: (i) $N_2O_4 \rightleftharpoons NO_2 + NO_2$, (ii) $N_2O_4 \rightleftharpoons NO_2^+ + NO_2^-$, and the mode which predominates is determined by the dielectric constant of the medium (Waters, *J.*, 1942, 153).

(i) *Homolytic dissociation.* If atom transfer follows this mode, it must result from impact between NO_2 molecules, a type of reaction which occurs also in the equilibrium $2BrF_3 \rightleftharpoons BrF_2^+ + BrF_4^-$ (Banks, Emeléus, and Woolf, *J.*, 1949, 2861). A molecule having the structure proposed by Longuet-Higgins (*Nature*, 1944, **153**, 408) could serve as an intermediate, thus

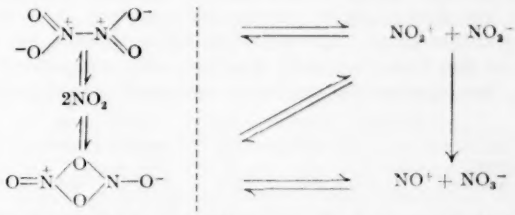


Since no dipolar constituent is present in the gaseous state (see below), an intermediate compound of this structure is more likely than the unsymmetrical molecule $ON{\cdot}O{\cdot}NO_2$ considered by Seel (*Z. anorg. Chem.*, 1952, **269**, 103). The existence of an intermediate compound having a different structure from the parent molecules has a direct analogy in dinitrogen trioxide (Addison, Lewis, and Thompson, *J.*, 1951, 2838). This interpretation however is incomplete, since it does not provide any reason why these particular ions should be formed.

(ii) *Heterolytic dissociation.* The extent of ionic dissociation of N_2O_4 broadly follows the ε ranges suggested by Waters (*loc. cit.*). Thus, in pure dinitrogen tetroxide ($\varepsilon = 2{\cdot}42$), ionic dissociation occurs to the extent of only about 0·1%; the rate of reaction with metals is decreased by the dilution factor only on dilution of the tetroxide with liquids (*e.g.*, benzene) of similar low dielectric constant. In glacial acetic acid ($\varepsilon = 7{\cdot}1$) containing sodium acetate, ionic dissociation is increased sufficiently to enable the presence of ions to be detected by electrolysis (Angus, Jones, and Philips, *Nature*, 1949, **164**, 433). The addition of diethylnitrosamine ($\varepsilon = 42{\cdot}5$) increases the electrical conductivity of liquid dinitrogen tetroxide by a factor of 10^8 (Part VI, *J.*, 1951, 1303). In solution in pure nitric acid, dinitrogen tetroxide is completely dissociated into ions (Goulden and Miller, *J.*, 1950, 2620), and in sulphuric acid ($\varepsilon = 110$; Brand, James, and Rutherford, *J. Chem. Phys.*, 1952, **20**, 530) ionisation is again complete (Gillespie, Graham, Hughes, Ingold, and Peeling, *J.*, 1950, 2504).

Such dissociation reactions involve a simple change from equal to unequal sharing of the bonding electrons, so the first stage in the heterolytic dissociation of dinitrogen tetroxide gives rise to NO_2^+ and NO_2^- ions. Detailed studies in each of the above liquid systems have identified the ions present as NO^+ and NO_3^-; the reaction $NO_2^+ + NO_2^- \longrightarrow NO^+ + NO_3^-$ must therefore follow immediately the primary heterolytic dissociation, and be irreversible. The high oxidising power of the nitronium ion, and its close proximity to the nitrite ion in the $[NO_2^+][NO_2^-]$ ion-pair would render the two groups incompatible. Oxygen-atom transfer is then an oxidative process which is consistent with the chemical properties of the ions concerned. Since it is the initial heterolytic dissociation, and not the oxidative process, which is influenced by ε of the medium, the ultimate ionic products of dissociation are independent of medium.

The equilibria existing in dinitrogen tetroxide may then be represented by the following scheme :



All the equilibria shown occur in the liquid state; only those to the left of the vertical broken line occur in the gaseous state. The complete absence of nitrite ion as a reaction product indicates that the oxidation of NO_2^- by NO_2^+ takes place before either ion is able to react independently with other reactants introduced into the system. Reactions with ethylenic linkages can be explained on the basis of the polar nature of the nitrogen in the tetroxide (Levy and Scaife, *J.*, 1946, 1093) without assuming the existence of discrete NO_2^+ and NO_2^- ions (Ingold, *Nature, loc. cit.*); it is significant that dinitro-compounds are formed in gaseous reactions also, when no ion-pairs exist. The possibility that nitronium and nitrite ions are produced on impact is not supported elsewhere in the chemistry of dinitrogen tetroxide.

(c) *Reaction of Metals with Gaseous Dinitrogen Tetroxide.*—In their study of gaseous N_2O_4–NO_2 mixtures, Williams *et al.* (*loc. cit.*) determined the value of μ_{NO_2} for a range of pressures and at a single temperature. The values of μ_{NO_2} and $\mu_{N_2O_4}$ were constant and independent of pressure, indicating that only these two components are present in the gaseous phase. The concentration of a third ionic component would vary with pressure, and its presence would lead to variations in μ_{NO_2} and $\mu_{N_2O_4}$. The same conclusion follows independently from a consideration of the low dielectric constant in the gaseous state.

If a second mechanism, involving N_2O_4 and NO_2 molecules only, operates in the liquid state, then reaction with gaseous mixtures (which contain no ion-pairs) should follow the same mechanism to give the same reaction products as with the liquid. When sodium is burnt in the gas (Holt and Sims, *J.*, 1894, **65**, 432; Dulong, *Ann. Chim. Phys.*, 1816, **2**, 317) a mixture of sodium nitrite and sodium nitrate is produced. At the temperature of burning sodium the gaseous phase contains oxygen and nitric oxide, and reaction with the latter gives rise to nitrite (following paper). At 300°, metallic zinc is converted into zinc oxide by nitrogen dioxide (Sabatier and Senderens, *Compt. rend.*, 1892, **115**, 236). The reaction of metallic sodium and zinc with gaseous N_2O_4–NO_2 mixtures has therefore been studied at temperatures below 140° (at which temperature dissociation of NO_2 becomes appreciable).

(i) The gas mixture was passed, at 60—80° and at atmospheric pressure, over metallic sodium. During about 15 min. the metal acquired a thin coating of white solid; after this, the coating was sufficiently cohesive to prevent further reaction. The coating was scraped from the metal, and its *X*-ray powder photograph was found to be identical with that of pure sodium nitrate.

(ii) The gas mixture was passed, at 120—140°, over a block of pure zinc. The metal developed a crust of white solid, which did not inhibit the reaction. Spectrophotometric analysis of the product showed the absence of nitrite, and chemical analysis confirmed that the product was pure zinc nitrate. A similar reaction, carried out at 60—80°, gave a yellow viscous liquid identical with a mixture of zinc nitrate and the compound $Zn(NO_3)_2,2N_2O_4$ (Part VII, *J.*, 1951, 2829). When this product was heated at 100°, dinitrogen tetroxide was evolved and pure zinc nitrate remained. At the temperature (300°) used by Sabatier and Senderens (*loc. cit.*) anhydrous zinc nitrate decomposes rapidly to zinc oxide (Part VII, *loc. cit.*).

Since the products of reaction in the gaseous and in the liquid state are identical, it is permissible to consider a mechanism of reaction in the liquid state which does not involve ion-pairs.

(d) *Stability of Nitrites in Gaseous Dinitrogen Tetroxide.*—The close analogy drawn above between reactions in the liquid state, and in the gaseous state below 140°, is only justified if nitrites are also stable in contact with gaseous N_2O_4–NO_2 mixtures over a corresponding temperature range. Oswald (*Ann. Chim.*, **1914**, **1**, 44) found that oxidation occurred at 100°, and also took place very slowly at room temperature. This reaction has been re-examined; the experimental conditions and results are given below:

Expt. No.	1	2	3	4	5	6	7
Temp.	40°	70°	85°	100°	100°	122°	200°
Reaction period (hours)	6	6	40	7	7	43	3
% conversion into nitrate	0·0	0·0	0·85	0·5	0·0	5·4	49·5

The nitrate content of the product was determined by ultra-violet spectrographic analysis (*J.*, 1952, 338). At the lower temperatures the oxidation of nitrite is negligible over long periods, although on prolonged contact (Expt. 3) slight oxidation does occur. At temperatures above the dissociation temperature of nitrogen dioxide (Expt. 7) oxidation is considerable; reactions of this type are considered in detail in the following paper. The dissociation temperature of the NO_2 molecule is normally quoted as 140°, but Expt. 6 implies that slight dissociation occurs below this temperature.

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385. *The Liquid Dinitrogen Tetroxide Solvent System. Part XIV.* Reactions of Sodium, Calcium, and Zinc Oxides with Dinitrogen Tetroxide and its Thermal Dissociation Products.*

By C. C. Addison and J. Lewis.

The following reactions have been studied: (*a*) The reactions of calcium and zinc oxides, and of sodium peroxide, with liquid dinitrogen tetroxide; the metal nitrate is the only salt produced in each reaction, and nitrites are not formed as intermediates. (*b*) The reaction of the three oxides with nitrogen dioxide gas at temperatures up to 140° and for various periods of contact; the products are the same as with the liquid tetroxide. (*c*) Corresponding reactions at temperatures above 140° are more rapid, and produce nitrite as well as nitrate. The quantity of nitrite decreases with increase in temperature; at constant temperature the quantity of nitrate increases, at the expense of nitrite, with duration of contact. (*d*) The effects observed in (*c*) have been explained on the basis of the ready reaction between the oxides and nitric oxide to produce nitrites, and by the oxidation of these to nitrates, which occurs in the high-temperature range only.

These experiments were initiated in order to determine the conditions under which metal oxides react with dinitrogen tetroxide, since oxides have been postulated (Part VIII, *J.*, 1951, 2833) as intermediates in the metal–dinitrogen tetroxide reaction mechanism which predominates at higher temperatures. It was soon established that reaction does occur to give products in agreement with the postulated mechanism. However, much of the evidence in the literature on reactions between metal oxides and dinitrogen tetroxide is contradictory, especially where the thermal dissociation products of the tetroxide are not taken into account. A detailed investigation has therefore been carried out into these reactions.

Calcium oxide has been stated to give a mixture of nitrate and nitrite with nitrogen dioxide gas at room temperature (Oswald, *Ann. Chim.*, **1914**, **1**, 44), at 180° (Partington and Williams, *J.*, **1924**, **125**, 947), and over the temperature range 15—300° (Briner,

* Part XIII, preceding paper.

Lugrin, and Monnier, *Helv. Chim. Acta*, 1930, **13**, 64). Anhydrous uranium oxides give uranyl nitrate on reaction with nitrogen dioxide for some hours at 90° under 14 atm. pressure (Gibson and Katz, *J. Amer. Chem. Soc.*, 1951, **73**, 5437). Reaction between barium oxide and nitrogen dioxide (Dulong, *Ann. Chim. Phys.*, 1816, **2**, 317) was found to give a mixture of nitrate and nitrite. Muller (*Annalen*, 1862, **122**, 1) states that oxides react to give nitrate uncontaminated with nitrite, whereas Briner *et al.* (*loc. cit.*) claim that oxides give nitrite as well as nitrate in liquid dinitrogen tetroxide.

The experiments described below leave no doubt that, in these reactions, nitrite does not occur in the product so long as the N_2O_4 and NO_2 molecules are the only species present, and is only formed at temperatures where the dissociation $NO_2 \longrightarrow NO + \frac{1}{2}O_2$ is appreciable; the nitrite does not therefore result from primary attack by nitrogen dioxide. Harcourt (*J.*, 1861, 267) found the oxides of the alkali metals to react with nitric oxide to give the nitrites. Reactions of liquid dinitrogen tetroxide may therefore be compared with reactions in the gaseous state provided that the latter are carried out at temperatures not exceeding about 140°. The upper temperature limit at which reactions have been studied is determined by the decomposition temperature of the products; some relevant values are given below:

Compound	$Zn(NO_3)_2$	$Ca(NO_3)_2$	$Ca(NO_2)_2$	$NaNO_3$	$NaNO_2$
Decomposition detectable at	160°	450°	230°	380°	320°
Decomposition rapid at	240	500	360	—	—

Lack of correlation with decomposition temperatures is responsible for apparently contradictory reports on reaction products; *e.g.*, Gmelin (see Mellor, "Treatise, etc.," Vol. II, p. 486) claimed that sodium burns in nitrogen dioxide to give sodium monoxide, whereas Holt and Sims (*J.*, 1894, **65**, 432) found the product to be a mixture of nitrite and nitrate.

Reactions with Liquid Dinitrogen Tetroxide.—(a) *Calcium oxide.* On addition of the liquid, no apparent reaction occurred. After about 10 hours' contact at a temperature near the boiling point (21·3°), the liquid had become brown. On evaporation, the free-flowing powder remaining was pale green, owing to adsorbed dinitrogen tetroxide. The last traces of adsorbed tetroxide were difficult to remove; in these experiments the powder was heated at 100° for 24 hours, the colour reverting to white but change in weight being negligible. The product was then analysed (*a*) by ultra-violet spectrophotometer, and (*b*) by use of Devarda's alloy for total nitrogen content, and potassium permanganate to detect nitrite. In no case was nitrite found in the product; the reaction may be represented as $CaO + 2N_2O_4 = Ca(NO_3)_2 + N_2O_3$ (see Table 1).

TABLE 1. *Reaction of calcium oxide with liquid dinitrogen tetroxide.*

Expt. No.	1	2	3	4	5	6	7
Period of contact (hours)	16	16	30	40	40	44	44
% Conversion of oxide into nitrate...	22·4	27·4	35·1	44·0	44·4	23·0	54·0

In all experiments (except No. 6) it was necessary to replenish the dinitrogen tetroxide at intervals of about 8 hours. In Expt. 6 the liquid was kept at +10° and no replenishment was necessary. The smaller degree of conversion into nitrate in this case indicates that the reaction is temperature-dependent, although not to the extent suggested by the values in Table 1, since the addition of fresh tetroxide in the other experiments agitates the solid and may expose fresh oxide surfaces to attack by the tetroxide. The incomplete conversion of oxide into nitrate even on long contact is attributed to the cohesive nature of the calcium nitrate formed as a coating round each oxide particle. The rate of reaction of calcium metal with dinitrogen tetroxide diminishes rapidly for the same reason. It appears that the physical nature of those nitrates (*e.g.*, calcium and sodium) which do not form complex salts with dinitrogen tetroxide differs from those nitrates (*e.g.*, zinc) which form such complexes. The former are sufficiently cohesive to decrease (and even inhibit) reaction, whereas the latter have little cohesive character.

In the reactions of calcium metal and of calcium oxide, no intermediate formation of

nitrite can occur, since calcium nitrite is stable in liquid dinitrogen tetroxide. A sample immersed in the tetroxide at 20° for 7 days was recovered.

(b) *Zinc oxide.* Dry zinc oxide reacted on contact with liquid dinitrogen tetroxide; nitric oxide was evolved and the colour of the liquid changed through brown to green within a few minutes. The reaction continued for some hours at a slower rate, and may be represented as $ZnO + 4N_2O_4 = Zn(NO_3)_2,2N_2O_4 + N_2O_3$. At 20°, reaction is about 80% complete after 10 hours, and about 95% after 20 hours.

(c) *Sodium peroxide.* When sodium peroxide was added to liquid dinitrogen tetroxide, no discoloration of the liquid took place, even on long standing. The product was found to contain nitrate, but no trace of nitrite. The sodium peroxide used contained small amounts of carbonate and hydroxide as impurities. A separate study of the reaction of these compounds with liquid dinitrogen tetroxide showed that these impurities involve no complication of the sodium peroxide reaction, since sodium nitrate is the only salt produced. The extent of reaction of sodium peroxide at 20° for periods of contact up to 48 hours did not exceed 20%. The reaction is $Na_2O_2 + 2NO_2 = 2NaNO_3$.

Reactions with Gaseous Nitrogen Dioxide and its Dissociation Products.—(a) *Sodium peroxide.* Experimental results are given in Table 2. Below 140° reaction was slow, but the rate of conversion into nitrate increased with increasing temperature. Above 140°, reaction became more rapid and the results in Table 2 show three pronounced effects: (1) appreciable quantities of nitrite are produced above 140°: (2) at a constant temperature above 140°, the quantity of nitrite produced decreases (and the nitrate increases) with time; (3) the quantity of nitrite produced decreases with increase in temperature.

TABLE 2. *Reaction of sodium peroxide with gaseous nitrogen dioxide.*

Temp.	Period of contact (hours)	Conversion, %: into nitrate	into nitrite	Temp.	Period of contact (hours)	Conversion, %: into nitrate	into nitrite
40°	12	7·1	0·0	190°	1·5	49·0	33·5
100	6	12·5	0·0	200	1·75	53·3	27·3
134	44	28·4	0·0	200	2·75	81·5	10·2
170	5	22·7	23·9	250	5	77·8	7·2

Since nitrite is first produced at the temperature at which nitrogen dioxide dissociates into nitric oxide and oxygen, nitrite production may be attributed to the presence of nitric oxide (Table 3). In the range 100—140° there was no visible change in the

TABLE 3. *Reaction of sodium peroxide with nitric oxide.*

Temp.	Period of contact (hours)	Conversion, %: into nitrate	into nitrite	Temp.	Period of contact (hours)	Conversion, %: into nitrate	into nitrite
120°	1	0·0	3·5	200°	2	4·0	77·5
150	1	2·3	69·0	210	1	5·0	66·7

appearance of the solid. Above 150° reaction was rapid; the solid fused in the gas stream and resolidified as the formation of nitrite carried the composition of the mixture past the sodium peroxide–sodium nitrite eutectic. The reaction may be represented as $Na_2O_2 + 2NO = 2NaNO_2$, and the small amount of nitrate in the product is attributed to oxidation of nitrite by peroxide in the liquid melt. An important observation in these experiments is the considerable increase in rate and extent of reaction which takes place at about 140°: the fact that this takes place at the same temperature as that at which nitrogen dioxide dissociates may not be entirely coincidental, although there appears to be no physical property of the nitric oxide molecule which undergoes change at about this temperature. Again, the general behaviour of sodium peroxide in other systems does not show evidence of sharp changes in reactivity at this temperature. The appearance of nitrite in the reaction product above 140° (col. 4, Table 2) may be attributed to the dissociation of nitrogen dioxide at this temperature, but the large amounts of nitrite observed are due to the high rate of this reaction, which begins at the same temperature.

The decrease in nitrite content with time at a constant temperature above 140° (Table 2) is explained satisfactorily by the oxidation of nitrite to nitrate at these temperatures by nitrogen dioxide (Table 4). In order to determine the mechanism of

this high-temperature oxidation, the reactions of sodium nitrite with nitric oxide and with oxygen were examined. Oxygen was found to have no effect upon sodium nitrite over periods of 7 hours at 150°, and 9 hours at 270°. Nitric oxide did not react with sodium nitrite at temperatures between 150° and 270° for periods up to 5 hours. The oxidising powers of nitrogen dioxide are not therefore due to nitric oxide or oxygen molecules

TABLE 4. *Reaction of sodium nitrite with nitrogen dioxide.*

Temp.	Period of contact (hours)	$NaNO_2$, %, oxidised to $NaNO_3$	Temp.	Period of contact (hours)	$NaNO_2$, %, oxidised to $NaNO_3$
100°	7	0·0	170°	3·25	17·0
122	43	5·4	200	3	49·5
150	4	2·9	250	9	57·0
160	3	10·8	260	6	23·7

produced by dissociation. Since the reaction is so largely dependent upon temperature, it may be considered to arise from oxidation by atomic oxygen produced by impact at the solid surface of NO_2 molecules possessing the necessary thermal energy, thus: $NO_2 \longrightarrow NO + O$, followed by $NaNO_2 + O \longrightarrow NaNO_3$. Katz and Gruen (*J. Amer. Chem. Soc.*, 1949, **71**, 2106) suggest that atomic oxygen is the active species in the oxidation of the oxides U_3O_8 and UO_2 to UO_3 by nitrogen dioxide at 250—300°.

(b) *Calcium oxide.* Experimental results are given in Table 5. The trace of nitrite sometimes observed below 140° is probably due to adsorbed nitrogen dioxide. In these experiments a stream of nitrogen dioxide was passed over the calcium oxide, so the nitric oxide produced was removed continually from the system. In Briner, Lugrin, and Monnier's experiments (*loc. cit.*) the nitric oxide produced was retained in the system by the use of sealed tubes, and appreciable nitrite formation was observed. The experimental conditions are clearly important here, since we could not detect reaction between calcium oxide and nitric oxide below 140° at atmospheric pressure even in 3 hours.

TABLE 5. *Reaction of calcium oxide with nitrogen dioxide.*

Temp.	Period of contact (hours)	Conversion, % into nitrate	into nitrite	Temp.	Period of contact (hours)	Conversion, % into nitrate	into nitrite
124°	24	5·9	0·0	200°	1·5	39·3	7·4
124	45	8·3	0·2	230	1·5	44·0	3·0
134	24	9·0	0·4	260	1·5	52·3	1·2
134	46	19·3	0·2	260	4·25	54·2	0·6
170	3·25	35·7	10·3				

Above 140°, absorption of nitrogen dioxide by calcium oxide was relatively rapid, with the production of nitrite as well as nitrate, but the quantity of nitrite produced was much less than in the case of sodium peroxide. The nitrite content decreased with time and with increasing temperature; this is readily explained by the oxidation of calcium nitrite to nitrate by nitrogen dioxide, which Partington and Williams (*loc. cit.*) have found to occur slowly at 180° but rapidly at 280°. The low nitrite contents of the product will also be due partly to the fact that calcium oxide reacts only slightly with nitric oxide; the nitrite produced in this reaction is small compared with that produced by sodium peroxide (Table 3). The nitrite values given for experiments above 150° (Table 5) are minimum values, and the quantity of nitrite produced originally in the reaction will exceed these values. The concentration of nitric oxide in the gas stream in these experiments was much less than that employed in the calcium oxide–nitric oxide experiments, so over this higher temperature range the formation of nitrite cannot be attributed (as in the case of sodium peroxide) entirely to the presence of nitric oxide in the gas stream. The ready reaction of nitric oxide with peroxides suggests an additional process for the production of calcium nitrite; atomic oxygen formed by decomposition of nitrogen dioxide at high temperatures may oxidise calcium oxide to calcium peroxide, which then reacts directly with nitric oxide, *i.e.*, $CaO + O \longrightarrow CaO_2$, followed by $CaO_2 + 2NO \longrightarrow Ca(NO_2)_2$.

(c) *Zinc oxide.* Zinc oxide reacts readily with nitrogen dioxide. Below 100° the product was a viscous liquid identical with that produced on warming the complex $Zn(NO_3)_2,2N_2O_4$. When this was heated in a current of dry air at 100°, nitrogen dioxide

was evolved, leaving a mixture of zinc oxide and zinc nitrate. Reactions carried out above 100° gave a product free from combined nitrogen dioxide. In these reactions it was essential to remove all nitrogen dioxide from the atmosphere before allowing the temperature of the reaction mixture to fall below 100°, as the dioxide was rapidly absorbed by the zinc nitrate present. Over the available temperature range the reaction $ZnO + 3NO_2 = Zn(NO_3)_2 + NO$ is not greatly temperature-dependent, and is about 70% complete after 8 hours at 160°.

Experimental

Metal Oxide–Gas Reactions.—The solid reactant was contained in a silica boat, which was placed in a 25 cm. × 2·5 cm. Pyrex-glass combustion tube. The tube terminated in B19 ground joints, and was closed by a 2-way glass tap on the inlet end, and a straight tap on the outlet. For reaction temperatures below 140°, the combustion tube was contained in an electrically-controlled thermostatic oven. For higher temperatures the combustion tube was passed through a hole (1—2 mm. clearance) in a heated aluminium block, 15 × 10 × 10 cm. Two thermometers were placed in holes drilled to the centre of the block. The combustion tube was guarded by phosphoric oxide traps at each end. The solid was weighed in the pre-weighed boat enclosed in a stoppered weighing tube, then transferred directly to the combustion tube. Transfers were carried out in a dry-box. For reactions involving nitrogen dioxide, the combustion tube was evacuated, closed, and connected to a vessel containing liquid dinitrogen tetroxide. It was then heated to the required temperature, opened, and a steady current of nitrogen dioxide drawn over the boat. The stream of gas could be controlled more readily by application of a slight vacuum than by warming the liquid tetroxide. The tube was then closed at the inlet, evacuated, and allowed to cool. Dry air was admitted to the combustion tube, and the boat and contents were immediately transferred to a stoppered weighing tube. For reactions involving nitric oxide, the oxygen was removed from the apparatus by successively passing in dry nitrogen, and evacuating the vessel. The nitric oxide was passed through the combustion tube in a stream of dry nitrogen.

Materials. Calcium and zinc oxides were dried immediately before use by heating them at 600° for 1 hour, and cooling them in a vacuum desiccator. The zinc oxide was of A.R. quality; the calcium oxide was prepared by heating A.R. calcium carbonate in a silica boat at 1000° to constant weight.

The peroxide content of A.R. sodium peroxide was determined by hydrolysis in cold boric acid solution, and titration with potassium permanganate. A sample of the peroxide was hydrolysed, the hydrogen peroxide decomposed by boiling the solution in a flask fitted with a Bunsen valve, and the alkalinity determined by titration before and after precipitation of the carbonate. The sample used contained 6·2% of sodium carbonate and 0·7% of sodium hydroxide.

Anhydrous calcium nitrite was prepared as follows. About 1 g. of freshly precipitated silver nitrite was added to a suspension of a slight excess of calcium oxide in boiling water. The silver oxide was filtered off, and excess of calcium ions removed from the solution by treatment with carbon dioxide and boiling. The liquid was concentrated, and finally evaporated in a vacuum desiccator. On prolonged standing the yellowish-white hydrate of calcium nitrite was obtained. This was crushed and heated at 160° to remove water of crystallisation (Partington and Williams, *loc. cit.*); ultra-violet spectrophotometric analysis showed the product to be at least 97% pure.

Nitric oxide was prepared by reaction of 4N-sulphuric acid and solid sodium nitrite (Part IX, *J.*, 1951, 2838). The nitrogen dioxide was removed from the gas stream by passage through towers packed with activated alumina and with sodium hydroxide pellets, and the nitric oxide finally dried (P_2O_5).

Analysis of products. (a) ZnO–N_2O_4 Reaction. On warming, the product evolved dinitrogen tetroxide, giving a yellow viscous liquid which changed (after 3 hours' heating at 100°) into a white crystalline powder. This powder was partly soluble in water; the insoluble portion was identified as zinc oxide, and the solution contained zinc nitrate free from nitrite. Analysis of the powder gave Zn, 36·1; NO_3^-, 63·2% (Calc. for conversion of 92% of zinc oxide into zinc nitrate: Zn, 36·15; NO_3^-, 63·1%). Analysis of the original product (Part IX, *loc. cit.*) gave Zn, 19·1; NO_2^-, 24·0% [Calc. for 89·1% conversion of zinc oxide into $Zn(NO_3)_2.2N_2O_4$: Zn, 19·1; NO_2^-, 24·05%].

(b) Na_2O_2–NO_2 Reactions above 140°, and Na_2O_2–NO reactions. These reactions are

considered together, since both give rise to solid products which are mixtures of sodium peroxide, nitrite, and nitrate. The product was hydrolysed in water, and hydrogen peroxide decomposed by boiling the solution. The solution was then analysed for nitrate and nitrite content by ultra-violet spectrograph. Removal of hydrogen peroxide was essential since it absorbs strongly in the range 280—370 mμ. For accurate analysis of the nitrite content it was therefore necessary to confirm the stability of the nitrite ion in alkaline solution of hydrogen peroxide. A mixture of known quantities of sodium peroxide and sodium nitrite (with the latter about 5% of the mixture) was therefore dissolved in water, and the ultra-violet absorption spectrum of the solution determined immediately. In separate portions of the solution the hydrogen peroxide was then decomposed (i) by boiling the solution and (ii) by keeping it for a week. In each case the absorption spectrum of the resulting solution confirmed that there was no change in its nitrite content.

In all the above reactions the increase in weight of the solid was determined accurately, and was found to correspond to the nitrate and nitrite produced in the reaction. This excludes the possibility of the formation of salts of other nitrogen oxy-acids.

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386. *Ion-exchange in Crystals of Analcite and Leucite.*

By R. M. BARRER and L. HINDS.

The exchange reactions of analcite and leucite have been investigated quantitatively at low temperatures for the ion pairs Na–K, Na–Tl, Na–Rb, K–Tl, Tl–Rb, and Na–Ag. In most of these systems it was found that when several partly exchanged analcites or leucites were treated with identical exchanging solutions the end-points depended upon the initial compositions and previous histories of the analcites. The exchange isotherms for Na–K, Na–Tl, and K–Tl showed evidence of limited mutual solid solubility of the end-members in the exchange, and this was further established by optical, analytical, and *X*-ray methods. Exchange isotherms for Na–K show hysteresis. The dependence of both hysteresis and end-points on the initial composition of exchanger finds a natural explanation in terms of nucleation phenomena associated with mutual limited solubility of the end members.

The rates of exchange follow the $\sqrt{t}$ diffusion law. The kinetics for Tl–Na have been analysed in terms of two $\sqrt{t}$ diffusion equations, and values of the ion-exchange diffusion coefficient obtained. The Arrhenius energy of activation is 14,900 cal./g.-ion. The $\sqrt{t}$ law has been correlated with the nucleation and limited solid solubility phenomena.

Lithium analcite and analcites containing bivalent cations have previously proved very difficult to prepare. However, a lithium-rich and a lead-rich analcite have now been obtained. The lead appears to enter the crystals as a univalent complex $PbOH^+$.

MOST contemporary effort in the study of ion-exchange is concerned with gels and resins. Gels, whether inorganic or organic, are in some ways less satisfactory for the quantitative study of ion-exchange than crystals, which provide a definite exchanger framework, and may be chosen according to a number of crystal chemical properties. Crystalline exchangers include such layer-lattice minerals as clays and micaceous products (montmorillonite, illite, vermiculite) and also aluminosilicates with robust three-dimensional anionic networks (analcite, leucite, cancrinite, nosean, sodalite, chabazite, mordenite, and harmotome). From the latter group of crystals one may seek an exchanger with a charged, sieve-like three-dimensional anion, Z, wholly inert and rigid, into which cations may be inserted on identical sites, thereby displacing their electrochemical equivalent of other cations. The end-members for a pair of cations A and B would be AZ and BZ, and could then form a continuous range of ideal solid solutions.

A statistical thermodynamic approach to this model has been outlined (Barrer, "Colloque Internat. sur les Réactions dans l'État Solide," Paris, 1948, CNRS). For a

reaction between the exchanger and two immiscible solid salts, AX and BX, each in equilibrium with its saturated solution :

$$AX_{solid} \rightleftharpoons AX_{sat.\ aq.};\quad BX_{solid} \rightleftharpoons BX_{sat.\ aq.}$$

$$AX_{sat.\ aq.} + BZ \text{ (in solid solution with AZ)} \rightleftharpoons BX_{sat.\ aq.} + AZ \text{ (in solid solution with BZ)}$$

and for an anhydrous exchange medium (sodalite, ultramarine, nosean) the mol.-fractions N_A and N_B in the exchanger at equilibrium will be given by :

$$\frac{N_A}{N_B} = \frac{(j_{BX})^2 j_A}{(j_{AX})^2 j_B} \exp\left[-(E_{AX} - E_{BX} + \Delta E_{B,A})/RT\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Where the exchange medium is hydrated, but the number of water molecules is not altered by exchange (chabazite, mordenite)

$$\frac{N_A}{N_B} = \frac{(j_{BX})^2 j_A j_{H_2O,A}}{(j_{AX})^2 j_B j_{H_2O,B}} \exp\left[-(E_{AX} - E_{BX} + \Delta E_{B,A} + \Delta E_{H_2O})/RT\right] \quad . \quad . \quad . \quad . \quad (2)$$

Finally, where the water of hydration of the exchange medium is displaced into the solution (analcite)

$$\frac{N_A}{N_B} = \frac{(j_{BX})^2 j_A j_{H_2O,A}}{(j_{AX})^2 j_B j_{H_2O}} \exp\left[-(E_{AX} - E_{BX} + \Delta E_{B,A} + \Delta E'_{H_2O})/RT\right] \quad . \quad . \quad . \quad . \quad (3)$$

In these expressions j_{BX}, j_{AX} are the partition functions of the salts BX and AX; j_B, j_A are the partition functions for the cations B and A in their environment within the zeolite; $j_{H_2O,B}$ and $j_{H_2O,A}$ are these functions for intracrystalline water in association with A and B cations; and j_{H_2O} is the partition function of a water molecule in the saturated solution, respectively. E_{AX} and E_{BX} are the lattice energies of AX and BX; $\Delta E_{B,A}$ is the energy of replacement of A by B cations in the zeolite; ΔE_{H_2O} is the change in binding energy when A is replaced by B in the crystal; and $\Delta E'_{H_2O}$ is the energy of displacement of water from the crystal into the solution. It may be a reasonable approximation to replace any partition function $j(T)$ by $(kT/h\nu)$ where ν denotes the Debye frequency.

Equations (1)—(3) show several factors which determine the equilibrium points. Since lattice energies are known for many salts, in such a crystalline exchanger the energies of replacement of one cation by another might be found. Binding energies of water molecules can be determined from the change with temperature of the equilibrium water vapour pressure over crystals of the exchanger. It is, however, quite unknown whether even the robust framework aluminosilicates approach the conditions required for the validity of equations (1)—(3).

In any study of solid-state reactions, equilibrium and kinetic measurements will both be of significance. For ion-exchange the appropriate rate constant is the intracrystalline ion-exchange diffusion coefficient. No such diffusion coefficients have yet been determined for exchanges involving crystalline aluminosilicates, although any rational theory of ion-exchange must await the collection and analysis of such data. A study of ion-exchange in crystals has therefore been initiated in these laboratories with sodalite–nosean minerals and zeolites to study quantitatively exchange equilibria and kinetics as a simple type of solid-state reaction. The present work concerns exchange reactions of analcite and leucite. Considerable attention has recently been paid to some aspects of ion-exchange in analcite, mordenite, and chabazite (Barrer, *J.*, 1948, 2158; 1950, 2342) and in other species (Barrer and White, *J.*, 1951, 1167). Analytical and *X*-ray data have been obtained, and some quantitative conclusions reached. However, in these studies equilibrium and kinetic measurements were not the immediate objectives.

Experimental

Most exchanges were carried out in sealed glass tubes, which had first been boiled for 2—3 hr. in distilled water. The tubes with their charge of solid reactants and some water were clipped on to a slowly rotating plate in an air-thermostat. For experiments at high temperatures, stainless-steel autoclaves were used (Barrer, *J.*, 1948, 127). These had an internal capacity of ~20 ml., and were sometimes employed with thin silver tubes as inserts,

to prevent contact of reactants with the steel walls. In other measurements the reactants were sealed in the glass tube, and the latter was placed inside the steel autoclave. A little water was then added to the autoclave, before sealing it, to act as pressure equaliser. It was then possible to carry out reactions in glass up to 150°, but above this temperature attack of the glass occurred. In other experiments exchange reactions were carried out with fused salts, such as potassium thiocyanate and thallous nitrate. Reactions were examined in the range 200—300° in the air thermostat.

The degree of exchange was measured in three ways: (*a*) by an ignition method, (*b*) by a weighing method, and (*c*) by chemical analysis. In a previous study (Barrer and G. Styan, unpublished) it was found in the reaction

$$\text{Na-analcite} + K^+, \text{aq.} = \text{K-analcite (leucite)} + Na^+, \text{aq.} + H_2O$$

that the extent of the exchange of sodium by potassium could be measured by the amount of water lost from the original analcite during exchange (Fig. 1*b*). The water content of the synthetic analcites was 8·46%, and that in leucite made from analcite by repeated treatments

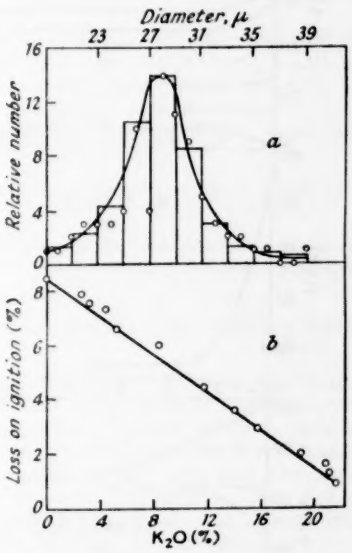


FIG. 1*a*. *A typical size-distribution curve of crystals of synthetic analcite.*

FIG. 1*b*. *Relation between water content and potassium oxide content of crystals intermediate in composition between analcite and leucite.*

with potassium chloride was 0·75%. These two points were joined by a straight line (Fig. 1*b*) and this line gave the relation between loss in weight on ignition and the sodium and potassium contents. The circles give Barrer and Styan's analytical results.

Other ion-exchanged analcites besides leucite are anhydrous (*e.g.*, the Tl, Rb, Cs, and NH_4 forms as shown by Barrer, *J.*, 1950, 2342). The differences in weights of such cation pairs as Na–Tl, K–Tl, or Na–Rb are sufficient to allow the extent of exchange to be measured by weighing the exchanger before and after reaction (with due allowance for changing water content). In the third method of following the exchange (*c*, above) the procedures employed were standard ones, the silica and alumina being determined after decomposition of the mineral with fusion mixture, and the sodium and other alkali metals by the Lawrence Smith method (*e.g.*, Vogel, "Quantitative Analysis," Longmans Green and Co., 1939, p. 664). Thallium was estimated by an adaptation of the Andrews potassium iodate titration (*idem*, *ibid.*, p. 438): $KIO_3 + 2TlCl + 6HCl = KCl + 2TlCl_3 + ICl + 3H_2O$. Lead in lead analcite was estimated after removal of silica by treatment with hydrofluoric acid solution. The residue was extracted with acetic acid, and the extract diluted and filtered. After dilution to 200 ml. the solution was heated to boiling, and the lead determined as chromate.

Ion-exchange and recrystallisation products were examined optically, a Leitz polarising microscope and a Vickers projection microscope being used. Reactions were also followed by *X*-ray powder photography, a Hilger HRX unit with Cu-$K\alpha$ radiation being used. This

method served not only to compare the exchange products but also to detect and characterise metamorphic minerals * which sometimes crystallised in place of the expected simple ion-exchanged analcites. Unit-cell determinations were effected with the aid of Bjurstrom charts.

In order to measure ion-exchange diffusion coefficients it was necessary to determine the external surface area of the crystallites. For this purpose, Kozeny's method was employed, degassed distilled water being used as flowing liquid (*e.g.*, Carman, *Discuss. Faraday Soc.*, 1948, **3**, 72). The area S of the bed of crystallites is then given by $S = \sqrt{\varepsilon^3 \Delta p / k\eta v L}$, for a liquid of viscosity η flowing under a pressure head Δp at velocity v through the bed of depth L; ε is the void volume in c.c. per c.c. of the bed, and $k = 5$ is Kozeny's constant.

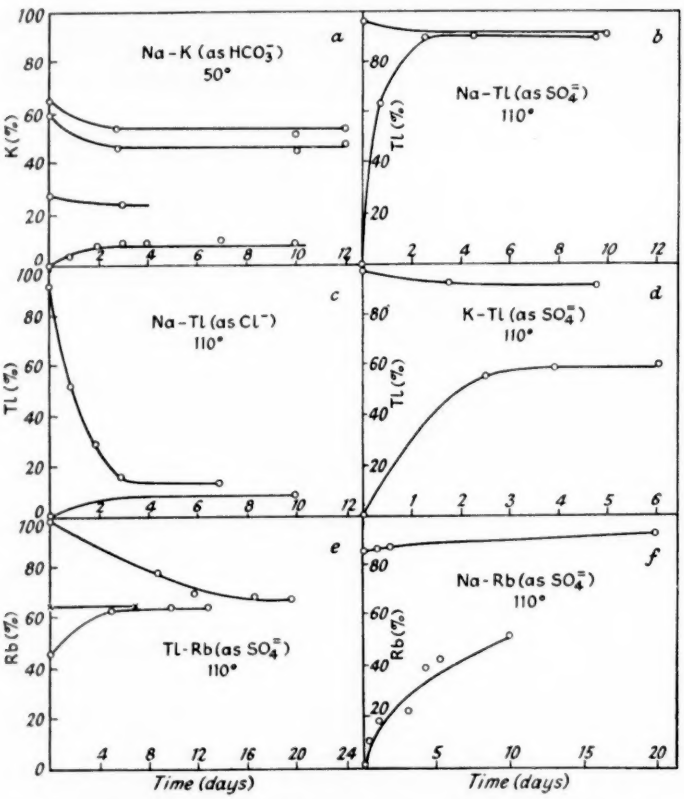


FIG. 2. *Variation of end-point with initial composition of crystals for exchanges involving solutions mutually saturated with each of a pair of salts.*

The analcite used in this work was synthesised hydrothermally from gels of composition $Na_2O,Al_2O_3,4SiO_2,xH_2O$ made by mixing sodium aluminate suspensions with silicic acid gel suspensions. Experimental conditions were varied in order to try to control the crystal sizes by (*a*) different rates of heating, (*b*) addition of sodium carbonate solution to raise the pH, (*c*) dilution, (*d*) seeding with analcite crystals, (*e*) alteration of reaction temperature between 200° and 300°, and (*f*) variation of the time of reaction. Although the extent of crystallisation could be affected especially by conditions (*b*), (*e*), and (*f*), no certain method of controlling the size of the crystals emerged. The size distribution among the crystallites in a typical preparation is shown in Fig. 1*a*. Occasionally, relatively uniform crystal sizes appeared. Since,

* These and other recrystallisation reactions will be described later (Barrer, Hinds, and White, *J.*, in preparation).

however, no certain uniformity could be achieved the following results were obtained with sieved crystals, which were nevertheless heterogeneous in diameter.

Preparation of Lithium and Lead Analcite.—Barrer (*J.*, 1950, 2342) found that although analcite gives K, Rb, Tl, NH_4, and Ag forms by direct exchange with the sodium form, yet it was not possible to introduce significant amounts of Li, or of bivalent cations such as Ca or Ba. We have now been able to prepare analcites enriched in both lithium and lead by the following methods.

The silver form of analcite was obtained by heating analcite in fused silver nitrate. This was then treated at 110° with a concentrated brine of lithium chloride. Any silver displaced formed an anionic complex such as $Li[AgCl_2]$, and the concentration of free silver ion fell so low that reaction proceeded in the direction

$$Ag_2O,Al_2O_3,4SiO_2,2H_2O + 4LiCl,\ aq. = Li_2O,Al_2O_3,4SiO_2,2H_2O + 2Li[AgCl_2]$$

until extensive exchange was effected. Lithium analcite proved to be hydrated and possessed a cubit unit cell of $13{\cdot}5_0$ Å edge (to compare with $13{\cdot}6_7$ Å for the more expanded sodium form). The lithium analcite like sodium analcite was a sorbent towards small polar molecules such as ammonia.

Lead analcite was obtained by heating sodium analcite at 110° with saturated lead chloride, three treatments being given. The product gave an X-ray powder photograph with spacings characteristic of sodium analcite, indicating a cubic unit cell similar to that of sodium analcite. A certain amount of recrystallisation was also detected by optical examination.

The mineral freed of all lead chloride showed an increase in weight which, according to the reaction

$$x\mathrm{PbCl_2} + \mathrm{Na_2O,Al_2O_3,4SiO_2,2H_2O} = [x\mathrm{Pb},2(1-x)\mathrm{Na}]_2\mathrm{O,Al_2O_3,4SiO_2},2(1-x)\mathrm{H_2O} + 2x\mathrm{NaCl} + 2x\mathrm{H_2O} \quad . \quad (a)$$

would correspond to 94% exchange and to 34·4% of lead in the final product. However, two chemical analyses agreed in giving only 22·8% by weight of lead, so one must postulate a different mechanism of exchange :

$$2x\mathrm{PbCl_2} + \mathrm{Na_2O,Al_2O_3,4SiO_2,2H_2O} = [x\mathrm{PbOH},(1-x)\mathrm{Na}]_2\mathrm{O,Al_2O_3,4SiO_2},2(1-x)\mathrm{H_2O} + 2x\mathrm{HCl} + 2x\mathrm{NaCl} \quad . \quad (b)$$

For this mechanism the increase in weight requires 32% exchange. This corresponds to 22·6% by weight of lead in the final product as compared with 22·8% actually found. It therefore seems probable that lead enters the crystals as a univalent complex $(PbOH)^+$. Such a unit * might be expected to fill interstices in the aluminosilicate framework more than K^+ and about the same as (Na^+,H_2O) or (Ag^+,H_2O). This, taken in conjunction with only 32% exchange, may account for the observation that a sodium analcite series of lattice spacings, and not the potassium analcite (leucite) series to be expected for mechanism (*a*), was actually observed (silver and sodium analcites give very similar X-ray spacings; Barrer, *J.*, 1950, 2342).

Reversibility of Exchange Reactions.—If analcites are treated with a solution which is kept saturated with respect to both a sodium and a potassium salt, one might expect to find the same end-point whatever the value of x between 0 and 1 in the starting material of composition $[x\mathrm{K},(1-x)\mathrm{Na}]_2\mathrm{O,Al_2O_3,4SiO_2},2(1-x)\mathrm{H_2O}$. Several experiments were carried to test this not only for Na–K exchange but for a variety of other ion-pairs. The results of some of these in Fig. 2, *a*—*f*, show that the end-point may often vary with the value of x in the initial exchange medium. The figure also shows the rate of approach to the end-point of the reaction.

A summary of initial and final compositions of the exchanger is given in Table 1. Different Tl–Rb mixed analcites gave a single end-point from a solution kept saturated with respect to both thallium and rubidium sulphates; and the same was true of two Na–Tl mixed analcites at 110° when saturated sulphate solutions of these two cations were used. However, at 75° the end-point was not the same for the two mixed analcites, nor was it the same when the saturated chloride solution was used to effect further exchange (Table 1). Indeed, it was usual to find end-points which varied with the initial composition, often by a wide margin (Na–K; Na–Rb; K–Tl; Na–Ag). In the Na–Ag exchanges a side reaction consisting in deposition of silver makes the result uncertain, but no such uncertainty arises in the other systems. This notable variability of end-point is discussed later (p. 1888) and is seen to be a simple consequence of

* Radii of Pb^{++} and K^+ are 1·32 and 1·33 Å, respectively. The radius of Na^+ is 0·98 and of Ag^+ is 1·13 Å. Sodium and silver analcites are hydrated, but the potassium form is anhydrous (Barrer, *J.*, 1950, 2342).

nucleation phenomena arising in turn from limited solid solubility of end-members (*e.g.*, of $Na_2O,Al_2O_3,4SiO_2,2H_2O$ and $K_2O,Al_2O_3,4SiO_2$).

Exchange Isotherms.—Exchange isotherms were obtained on using solutions of constant total ionic strength and containing two electrolytes in various proportions. These are shown in Figs. 3, 4, and 5 for the Na–Tl, K–Tl, and Na–K pairs. For the first two exchanges the total molarity was 0·3 and the solution in each case was a mixture of the appropriate pair of salts. The end-points greatly favour the thallium-rich phase (Figs. 3 and 4). Both systems show substantial immiscibility between the extreme ion-exchanged forms, of a kind which will

TABLE 1. *End-points obtained when beginning with different compositions of exchanger.*

Initial cationic composition of analcite	Salts in satd. soltn.	Temp.	Final cationic composition of analcite
Na : K = 100 : 0	$NaHCO_3$ and $KHCO_3$	50°	Na : K = 92·1 : 7·9
Na : K = 72·2 : 27·8	$NaHCO_3$ and $KHCO_3$	50	Na : K = 75·9 : 24·1
Na : K = 41·1 : 58·9	$NaHCO_3$ and $KHCO_3$	50	Na : K = 52·8 : 47·2
Na : K = 36·1 : 63·9	$NaHCO_3$ and $KHCO_3$	50	Na : K = 46·3 : 53·7
Na : K = 100 : 0	$NaHCO_3$ and $KHCO_3$	110	Na : K = 33·8 : 66·2
Na : K = 17·1 : 82·9	$NaHCO_3$ and $KHCO_3$	110	Na : K = 41·2 : 58·8
Na : K = 4·1 : 95·9	$NaHCO_3$ and $KHCO_3$	110	Na : K = 5·5 : 94·5
Na : K = 1·4 : 98·6	$NaHCO_3$ and $KHCO_3$	110	Na : K = 4·2 : 95·8
Na : Tl = 100 : 0	Na_2SO_4 and Tl_2SO_4	110	Na : Tl = 9·0 : 91·0
Na : Tl = 4·2 : 95·8	Na_2SO_4 and Tl_2SO_4	110	Na : Tl = 8·7 : 91·3
Na : Tl = 100 : 0	Na_2SO_4 and Tl_2SO_4	75	Na : Tl = 13·4 : 86·6
Na : Tl = 9·6 : 90·4	Na_2SO_4 and Tl_2SO_4	75	Na : Tl = 9·8 : 90·2
Na : Tl = 100 : 0	NaCl and TlCl	110	Na : Tl = 91·9 : 8·1
Na : Tl = 8·7 : 91·3	NaCl and TlCl	110	Na : Tl = 86·8 : 13·2
Na : Rb = 100 : 0	Na_2SO_4 and Rb_2SO_4	110	Na : Rb = 48·1 : 51·9
Na : Rb = 15·3 : 84·7	Na_2SO_4 and Rb_2SO_4	110	Na : Rb = 6·5 : 93·5
K : Na : Tl = 98·6 : 1·4 : 0	K_2SO_4 and Tl_2SO_4	110	K : Tl = 39·6 : 60·4
K : Na : Tl = 0 : 3·1 : 96·9	K_2SO_4 and Tl_2SO_4	110	K : Tl = 7·6 : 92·4
Tl : Rb : Na = 96·9 : 0 : 3·1	Tl_2SO_4 and Rb_2SO_4	110	Tl : Rb = 64·5 : 35·5
Tl : Rb = 64·1 : 35·9	Tl_2SO_4 and Rb_2SO_4	110	Tl : Rb = 64·6 : 35·4
Tl : Rb = 46·2 : 53·8	Tl_2SO_4 and Rb_2SO_4	110	Tl : Rb = 63·8 : 36·2
Na : Ag = 100 : 0	Na_2SO_4 and Ag_2SO_4	75	Na : Ag = 45·8 : 54·2
Na : Ag = 8·4 : 91·6	Na_2SO_4 and Ag_2SO_4	75	Na : Ag = 62·4 : 37·6

now be considered in more detail for the Na–K exchanges. The latter were carried out by using a mixture of sodium and potassium chlorides in solutions of total molarity 3·5, and here the end-points favour the sodium-rich phase (Fig. 5). The isotherm has one and possibly two regions where large changes occur in the potassium content of the crystals for negligible or small changes in potassium content of the solution. According to the phase rule, an invariant region requires the co-existence of two solid phases and solution in equilibrium. The situation is, however, here complicated because one of these phases may develop on or in, and consume, crystallites of the other (see p. 1887). One of these phases is necessarily richer in sodium, the other in potassium. The isotherm for exchange going from sodium analcite to potassium analcite (leucite) does not coincide with that for the converse change from leucite to analcite, and a considerable hysteresis is observed. The behaviour is compatible with limited solid solubility of one ion-exchanged form of the crystal in the other. Limited solid solubility had previously been established for analcites at higher temperatures under hydrothermal conditions (Barrer and McCallum, *J.*, in preparation). It now seems that limited solid solubility extends to very low temperatures.

Direct evidence of two coexistent solid phases among partly ion-exchanged analcites was obtained in three different ways. First, this was made quite clear by optical examination. At the end-points of the reaction, crystals of two distinct refractive indices were observed side by side for the exchanges Na–K, Na–Tl, and K–Tl when the final composition of the solid lay within certain limits. A composition Na : K = 57·4 : 42·6 of the solid in the first immiscibility region for the Na–K exchange was next studied. It proved possible partly to separate crystals of the two kinds from this composition by sedimentation. One fraction gave on analysis Na : K = 64 : 36, and the other Na : K = 41 : 59. Finally, *X*-ray evidence of the two phases was obtained for Na–K and Na–Tl exchanges. If *continuous* solid solubility were encountered, *X*-ray powder photographs would show a continuous change from the pattern characteristic of

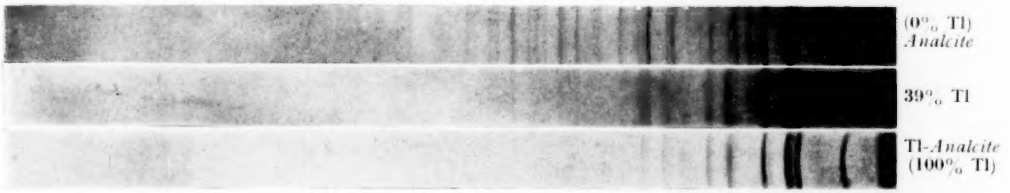


FIG. 6(*a*). *Stages in the conversion of* Na-*analcite into* Tl-*analcite. The intermediate* X-*ray powder photograph* (39% Tl) *shows simultaneous occurrence of* Na- *and* Tl-*analcite lines, and indicates two solid phases. The diffuseness of some of the lines for the intermediate composition* (39% Tl) *suggests small crystallites and nuclei, or some disorder.*

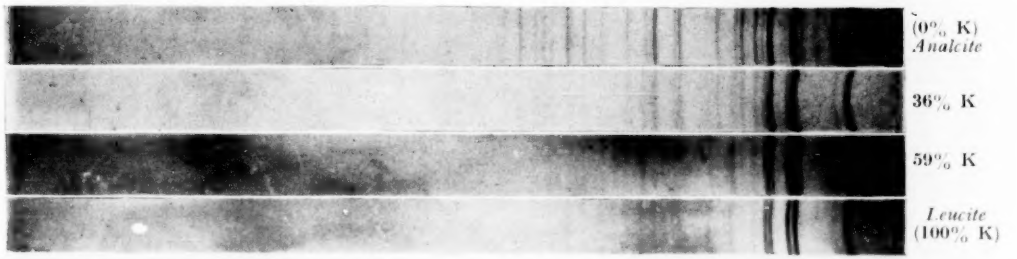


FIG. 6(*b*). *Stages in the conversion of* Na-*analcite into* K-*analcite (leucite). The* X-*ray powder photographs for intermediate compositions* (36% *and* 59% *exchange) show analcite and leucite lines side by side, and so indicate two co-existing solid phases, one rich in* Na *and the other in* K.

[To face p. 1856

one extreme form to that characteristic of the other. On the other hand, if two crystalline phases co-exist, the *X*-ray patterns of each phase will be present together, and a change in composition of the solid will result merely in weakening of the pattern of one form and the strengthening of that of the second form. *X*-Ray powder photographs show in fact this latter type of behaviour (Fig. 6).

FIG. 3.

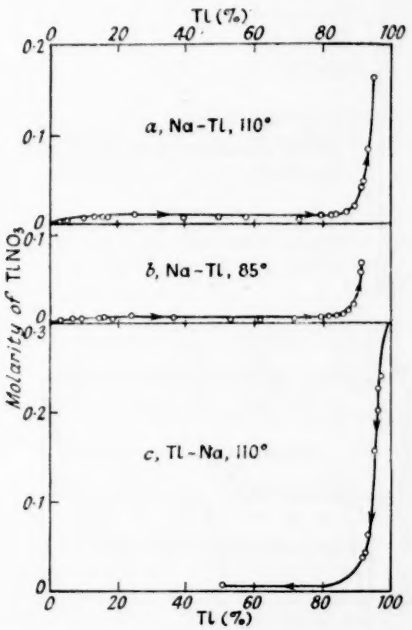


FIG. 4.

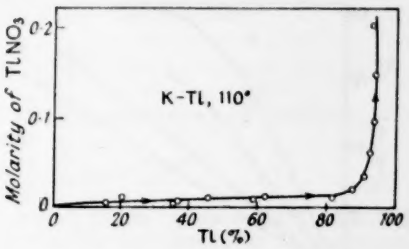
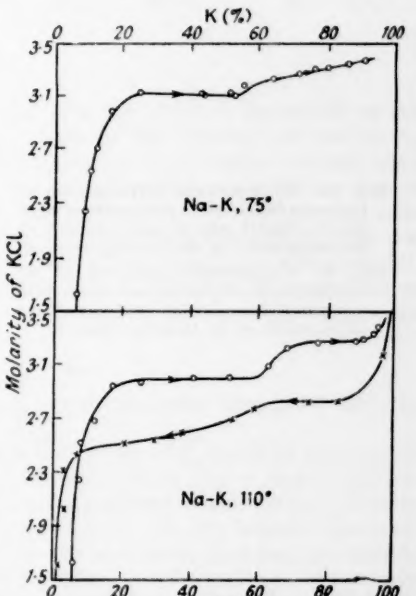


FIG. 3. *Typical exchange isotherms for* Na–Tl-*analcites. The total molarity of* $NaNO_3$ + $RbNO_3$ *is* 0·3M. *The isotherms give the molarity of* $TlNO_3$ *at the end-points as a function of* % *exchange of* Na *by* Tl *at* 110° *for the exchange approached from forward and reverse directions (Figs.* 3*a and c); and at* 85° *for the forward reaction (Fig.* 3*b).*

FIG. 4. *Exchange isotherm of* K- *and* Tl-*analcites in a solution of total molarity* 0·3M. *End-points are approached by the forward reaction (displacement of* K *by* Tl).

FIG. 5. *Exchange isotherms for* K–Na *in leucite–analcite system. The total molarity of the* NaCl + KCl *solution used is* 3·5M. *The isotherms at* 110° *and at* 75° *show the relatively invariant central section, and the isotherm at* 110° *shows also a substantial hysteresis.*

FIG. 5.



Exchange Kinetics.—The Na–Tl exchange kinetics were investigated at 75°, 85°, 95°, and 110°, samples of sodium analcite of surface area 2100 cm.²/g. being used in all runs. The exchanging pair of salts was Na_2SO_4 and Tl_2SO_4, and at all times sufficient of each salt was present to provide a saturated solution and an excess of the solid salts. Fig. 7 shows that over a considerable range of times and compositions of the solid a $\sqrt{t}$ diffusion equation is valid.

The application was first made of the simple diffusion law

$$Q_t/Q_\infty = (2A/V)\sqrt{Dt/\pi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

for diffusion in a medium of area A and volume V, where Q_t and Q_∞ are the amounts of exchange at time t and at infinite time respectively. This equation then gave for the diffusion coefficient $D = D_0 \exp(-E/\boldsymbol{R}T)$ the values in Table 2. The Arrhenius energy of activation E over the interval 75—110° was 14·9 kcal./g.-ion, as compared with $E \sim 13$ kcal./g.-ion calculated on the basis of equation (4) from earlier measurements on the Na–K exchange (Barrer and Styan, *loc. cit.*). The values of D in Table 2 require a correction on account of the limited mutual solid

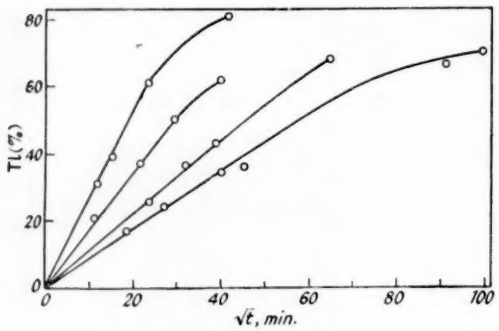


FIG. 7. *Some typical kinetic data for the* Na–Tl *exchange in leucite, showing the validity of the* $\sqrt{t}$ *diffusion law.*

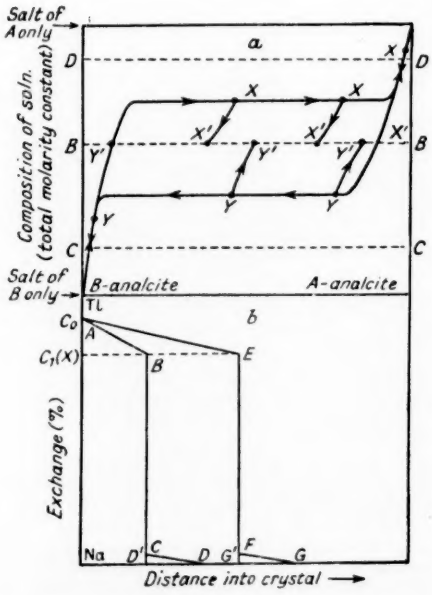


FIG. 8*a*. *Diagrammatic representation of hysteresis behaviour in ion exchange when there is limited mutual solid solubility of the end-members of the exchange reaction.*

FIG. 8*b*. *Concentration gradients in the crystals for two different times, when there is limited mutual solid solubility of the end-members of the exchange reaction.*

solubility of the sodium and thallium analcites. Concentration gradients inwards from the surface $x = 0$ of any crystal must have a concentration discontinuity as shown in Fig. 8*b*. The immiscibility gap of Fig. 3 is wide, and one may, to simplify the treatment of the system at

TABLE 2. *Exchange diffusion* Na–Tl.

Temp.	$10^{13}D$ (cm.² sec.⁻¹)	10^4D_0 (cm.² sec.⁻¹)	Temp.	$10^{13}D$ (cm.² sec.⁻¹)	10^4D_0 (cm.² sec.⁻¹)
110°	$4{\cdot}5_2$	1·43	85°	0·89	1·12
95	$2{\cdot}3_7$	1·68	75	0·63	1·44

110°, therefore neglect the sections CD or FG of Fig. 8*b*, corresponding to solubility of Tl-analcite in Na-analcite. The drop in thallium concentration along the lines AB and AE was

approximately from 91% Tl to 87% Tl (% of the total exchangeable ions). If the concentration at A is C_0 and at B or E is C_1, and ABD' and AEG' are taken to represent the concentration–distance curves, then it can be shown (Hermans, *J. Colloid Sci.*, 1947, **2**, 387; Danckwerts, *Trans. Faraday Soc.*, 1950, **46**, 701) that

$$[C_0 - C_1(X)]/C_1(X) = \alpha\sqrt{\pi}\exp\alpha^2\,\mathrm{erf}\,\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $\alpha = X_1/2\sqrt{D't_1} = X_2/2\sqrt{D't_2}$, X_1 and X_2 denoting the positions of the concentration discontinuities BD' and EG' at times t_1 and t_2, respectively. One then finds

$$Q_t = \frac{2A[C_0 - C_1(X)]}{\mathrm{erf}\,\alpha}\sqrt{\frac{D't}{\pi}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where D' denotes the exchange diffusion coefficient in the regions AB or AE. Since $Q_\infty/V = C_0$, one may now compare equations (4)—(6) to obtain

$$D/D' = \{[C_0 - C_1(X)]/C_0\,\mathrm{erf}\,\alpha\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Equation (5) was solved graphically for α, and C_0 and C_1 (X) being known (91% and 87%, respectively), the value of $D' = 6{\cdot}60 \times 10^{-12}$ cm.^{2} sec.$^{-1}$ at 110° was obtained. The magnitude of the correction for various values of $C_0 - C_1(X)$ (in % of total exchangeable ion) is given below for $C_0 = 91\%$:

$C_0 - C_1(X)$ (%)	$C_1(X)$ (%)	D'/D	$C_0 - C_1(X)$ (%)	$C_1(X)$ (%)	D'/D	$C_0 - C_1(X)$ (%)	$C_1(X)$ (%)	D'/D
0·25	90·75	104	6·0	85	9·3	10·0	81	5·8$_3$
1·0	90	37·2	8·0	83	7·2	15·0	76	3·9$_6$
4·0	87	14·6						

Discussion

Hysteresis in the exchange isotherms (*e.g.*, Fig. 5) is the result of the growth of one solid phase by nucleation in or on the other. Thus in the exchange of sodium by potassium, as the potassium concentration in the crystal grows, a stage is reached when the potassium ions begin to cluster and nuclei of a potassium-rich phase form and grow into crystallites on or in the sodium-rich matrix. In a system involving immiscible solid phases P_1 and P_2, one developing within or on the other, additional free-energy terms due to strain and interfacial surface tension must be added to the free-energy difference ΔG_1 which would arise between those amounts of separated phases of P_1 and P_2 containing an Avogadro number N_0 of cationic charges. For a nucleus containing i cationic charges, the free energy of formation is then

$$\Delta g = i\Delta G_1/N_0 + \Delta g_\sigma + \Delta g_s$$

where Δg_σ and Δg_s are the interfacial and strain free-energy terms associated with the formation of the nucleus of P_2 in or on a matrix of P_1.

For a fixed concentration of solution, where the bulk phase of P_2 would be more stable than that of P_1, $i\Delta G_1/N_0$ would be negative. However, the term $(\Delta g_\sigma + \Delta g_s)$ is positive. As i increases, Δg is at first positive and increases until it reaches a maximum (*e.g.*, Thomas and Staveley, *J.*, 1951, 2572), after which the negative term $i\Delta G_1/N_0$ becomes dominant and Δg decreases without limit as i increases. After this maximum, therefore, the nucleus would grow spontaneously. There will, owing to statistical size fluctuations, be a certain flux of nuclei past the critical size, followed by their spontaneous growth into crystallites. Hysteresis in such a system arises if the flux density of nuclei past the critical size has a very sensitive dependence upon the composition of the exchanging solution. This leads effectively to a concentration threshold below which the flux density of nuclei is negligible and above which it has a measurable value. For the growth of P_2 in a matrix of P_1 this threshold lies above that for thermodynamic equilibrium between solution and P_1 and P_2 in bulk, because of the free-energy term $(\Delta g_\sigma + \Delta g_s)$. For the growth of P_1 in a matrix of P_2 the threshold concentration lies for the same reason below that for the thermodynamic equilibrium between solution and bulk phases P_1 and P_2.

The exchange isotherm, according to the preceding model, will have the shape of Fig. 8*a*,

with two horizontal sections. If the properties of nuclei vary with their shape or with their position in or on the matrix, then finite flux densities of nuclei through the critical sizes will occur at different threshold concentrations for different groups of nuclei, and the horizontal sections of Fig. 8*a* will therefore become sloping to some extent. Such a state may be represented by Fig. 3.

On p. 1883 it was shown that the end-points in ion-exchanges of analcite often depend upon the initial cationic composition of the exchanger. This behaviour may be also traced to limited solubility and nucleation phenomena. One may consider an exchange isotherm as in Fig. 8*a*, obtained by using an exchanging solution of fixed total molarity (as in Figs. 3, 4, and 5). Conversion of B- into A-analcite follows the upper path, and the converse change follows the lower path in Fig. 8*a*. If the composition of the exchanging solution is kept constant during the exchange, as in Fig. 2, and so is represented by the line *BB*, and if the initial composition of the analcite corresponds to one of the three different points *X*, then the end-point must correspond to the appropriate one of the points *X'*. Similarly, with solids of compositions corresponding to the points *Y* on the lower curve the end-points are *Y'*. If the composition of the exchanging solution is represented by either line *CC* or *DD*, then, whatever the initial cationic composition of the analcite, the same end-point will be reached, independently of the past history of the specimen. The results of Table 1 and Fig. 2 can thus be readily interpreted.

The kinetics of exchange might at first be supposed, from the nucleation mechanism discussed, to give a sigmoid curve of Q_t/Q_∞ against t, as with barium azide and similar solids (*e.g.*, Garner and Southon, *J.*, 1935, 1705). However, the $\sqrt{t}$ diffusion law was observed instead. Nucleation can be expected to occur initially on or very near the surface of contact of each crystallite with the exchanging solution, which provides the necessary excess of the ion required for nucleation. However, lateral growth of nuclei over the surface must be much faster than the development in thickness, because the supply of ions by diffusion will be more rapid to surface layers than to deeper layers. Accordingly, nuclei form and develop quickly into a thin film of the new phase covering the old. Thereafter the boundary migrates into the crystal as in Fig. 8*b*, and the kinetics are governed by the $\sqrt{t}$ law.

It is now seen that the analcite framework does not give ideal solid solutions of one cationic form in the other, capable of leading to exchange equilibria as described in equations (1)—(3). One reason for this is that the aluminosilicate framework undergoes small but definite readjustments according to the size of the interstitial cations and according as they are hydrated or not (Barrer, *J.*, 1950, 2342). The radii of Tl^+ and Rb^+ are, however, virtually identical at 1·49—1·48 Å; neither ion-exchanged form is hydrated, and *X*-ray powder photographs give practically indistinguishable spacings (there are, of course, some differences in intensity of diffraction). It was therefore interesting that the end-points for three different initial cationic compositions of mixed $(Tl_2,Rb_2)O,Al_2O_3,4SiO_2$ are the same. Nevertheless, it was noted that at the end-points the crystals had become very finely divided. In other systems where crystal fracturing occurred this was definitely associated with nucleation and crystal growth of one phase on or in the other. Therefore the single end-point for Tl–Rb analcites in solutions saturated by both rubidium and thallium sulphates may arise merely because such solutions correspond in composition to lines such as *CC* or *DD* in Fig. 8*a*, and not because an immiscibility gap in the solid is absent. If this is so, limited mutual solid solubility of rubidium and thallium analcites must be attributed, not to structural differences in the anionic framework, but to another property such as a difference in the electro-positive character of the cations.

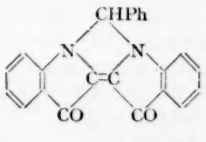
UNIVERSITY OF ABERDEEN. [*Received, January 27th*, 1953.]

387. *The Constitution of Ciba Yellow 3G.*

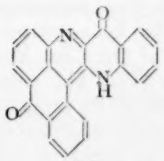
By R. S. Staunton and A. Topham.

It is shown that, of the five structural formulæ proposed for Ciba Yellow 3G, only one, *viz.*, formula (V), is consistent with the formation of the new degradation products (XII) and (XV). The structure of (XII) has been proved by its further degradation reactions, and the structure of (XV) by synthesis.

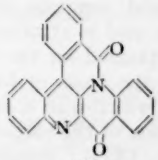
Ciba Yellow 3G is a vat dye first prepared by Engi (G.P. 249,145; *Z. angew. Chem.*, 1914, **27**, 144) by the action of benzoyl chloride, copper powder, and nitrobenzene on indigo. Its constitution has been investigated by numerous workers, and the following formulæ have been proposed: (I) (Engi, *loc. cit.*), (II) (Posner and Hofmeister, *Ber.*, 1926, **59**, 1827), (III) (Hope and Richter, *J.*, 1932, 2783), (IV) (de Diesbach, Bie, and Rubli, *Helv. Chim. Acta*, 1934, **17**, 113), and (V) (de Diesbach, Capponi, and Farquet, *ibid.*, 1949, **32**, 1214).



(I)

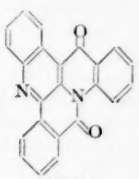


(II)

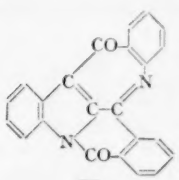


(III)

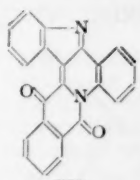
These formulæ were mostly based on a study of the degradative reactions, the most important of which may be summarised as follows. Ciba Yellow on vigorous oxidation with nitric acid yields phthalic acid. On fusion with sodium hydroxide it yields, *inter alia*, phthalic acid and indolo(3′ : 2′-3 : 4)quinoline. It dissolves in boiling sodium hydroxide solution with fission of a lactam group, to give the sodium salt of a monocarboxylic acid from which Ciba Yellow is regenerated by treatment with acid. This sodium salt is readily methylated to give a *N*-methyl-acid which cannot be cyclised but can be decarboxylated. The formula (VI) would also give a ready explanation of these reactions. Formulæ (I) and (II) are not those of lactams and so may be discounted. Substances (II) and (IV) were synthesised by de Diesbach and Miserez (*Helv. Chim. Acta*, 1948, **31**, 673) and by de Diesbach and Klement (*ibid.*, 1941, **24**, 158) respectively, and were different from Ciba Yellow. Formula (VI) is the only one which gives a ready explanation of the



(IV)



(V)

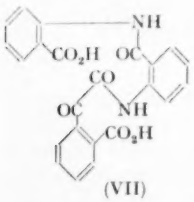


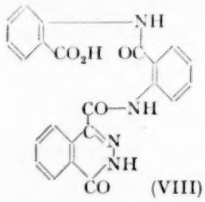
(VI)

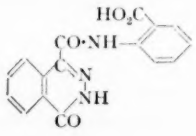
formation of indolo(3′ : 2′-3 : 4)quinoline on fusion with sodium hydroxide. This compound was first isolated from Ciba Yellow by de Diesbach, Bie, and Rubli (*loc. cit.*), who proved its constitution by a study of its further degradation reactions. It had however been synthesised already by Clemo and Perkin (*J.*, 1924, **125**, 1608). We repeated the work of these authors and proved the identity of the indoloquinoline from both sources (mixed melting point determination and *X*-ray powder photographs).

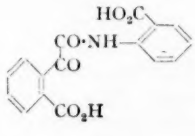
Ciba Yellow in sodium hydroxide solution was readily oxidised by permanganate at 20°, yielding a compound, $C_{23}H_{16}O_7N_2$, which titrated as a dicarboxylic acid and on hydrolysis yielded phthalonic acid and two mols. of anthranilic acid. This result disproved formula (III) and appeared to be most consistent with formula (VI), leading to the

formula (VII) for the permanganate degradation product. This degradation product was next treated under mild conditions with hydrazine: this should yield (VIII) if structure (VII) were correct. The product was, however, the compound (IX), condensation with hydrazine having been accompanied by loss of one mol. of anthranilic acid. The structure of (IX) was proved by synthesis: phthalonic anhydride and anthranilic acid yielded the


(VII)

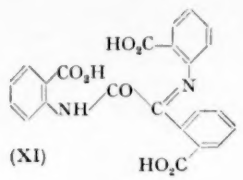

(VIII)

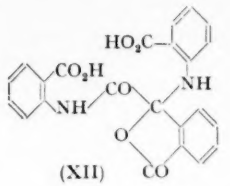

(IX)

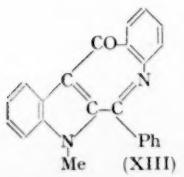

(X)

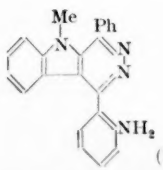
anilide-dicarboxylic acid (X), which with hydrazine gave (IX). The formation of compound (IX) from the permanganate degradation product with loss of one mol. of anthranilic acid suggests that in the permanganate degradation product one mol. of anthranilic acid is attached to the keto-group of the phthalonic acid fragment. This cannot be explained on the basis of the Ciba Yellow formula (VI), but can readily be explained on the basis of formula (V). The permanganate degradation product would then be (XI), which is in accord with all its properties except that it is only a dicarboxylic acid. Thus one of the carboxyl groups is probably involved in a cyclic "*pseudo*anilide" structure, *e.g.*, (XII): compounds of this type are well known (see, *e.g.*, Cornillot, *Ann. Chim.*, 1927, **8**, 120).

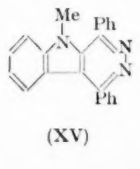
When the N-methyl-carboxylic acid from Ciba Yellow is decarboxylated (Hope and Richter, *loc. cit.*) and the product is heated with hydrazine a primary aromatic amine $C_{23}H_{18}N_4$ is obtained which on diazotisation and treatment with hypophosphorous acid yields a new base $C_{23}H_{17}N_3$. These results can be explained on the basis of the formula (V) for Ciba Yellow, leading to the formulæ (XIII), (XIV), and (XV) for the product of decarboxylation, the primary aromatic amine, and the base $C_{23}H_{17}N_3$ respectively. The


(XI)


(XII)

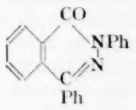

(XIII)


(XIV)

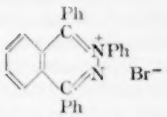

(XV)

structure (XV) was proved by synthesis. First it was shown that 1 : 2-dihydro-1-keto-2 : 4-diphenylphthalazine (XVI) on treatment with phenylmagnesium bromide gave 1 : 2 : 4-triphenylphthalazinium bromide (XVII) (compounds of this type are already known; see, *e.g.*, Thiele and Falk, *Annalen*, 1906, **347**, 114) which when heated with hydrazine yielded 1 : 4-diphenylphthalazine (XVIII). 3-Benzoyl-1-methylindole-2-carboxylic acid (XIX) was prepared both by the action of diphenylcadmium on 1-methylindole-2 : 3-dicarboxylic anhydride and by a Fischer indole synthesis from *N*-methyl-*N*-phenylhydrazine and ethyl benzoylpyruvate. Condensation of the keto-acid (XIX) with phenylhydrazine yielded 2 : 3-dihydro-3-keto-1′-methyl-2 : 6-diphenylindolo-

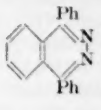
(2′ : 3′-4 : 5)pyridazine (XX). This on treatment with phenylmagnesium bromide gave 1′-methyl-2 : 3 : 6-triphenylindolo(2′ : 3′-4 : 5)pyridazinium bromide (XXI) which when



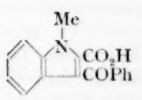
(XVI)



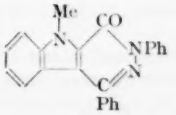
(XVII)



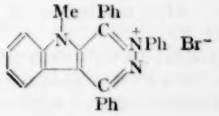
(XVIII)



(XIX)



(XX)



(XXI)

heated with hydrazine gave the required 1′-methyl-3 : 6-diphenylindolo(2′ : 3′-4 : 5)-pyridazine (XV), identical with that obtained from Ciba Yellow.

It is now clear that Ciba Yellow 3G is correctly represented by (V).

Experimental

Preparation of Ciba Yellow from Indigo.—Ciba Yellow used in this work was prepared as follows: Indigo powder (225 g.), copper bronze (22·5 g.), cuprous chloride (35·1 g.), benzoyl chloride (738 c.c.), and nitrobenzene (540 c.c.) were stirred at 160° ± 5° during 30 min. After cooling, the mixture was added to ethanol (540 c.c.) and kept overnight. The solid was filtered off, well washed with ethanol, and dried. The combined yield from three such experiments was boiled during 6 hr. with 4N-sodium hydroxide (4800 c.c.), more water being added as required to maintain the volume. The mixture was filtered hot through glass cloth, and the solid washed with hot dilute aqueous sodium hydroxide. The combined filtrate was acidified hot with 5N-hydrochloric acid (3780 c.c.). The solid was collected, washed with water, dried, and recrystallised from pyridine (3 l.) (yield, 88 g.; m. p. 277—279°). By re-boiling the solid which had not dissolved in the pyridine with the pyridine filtrate from the first crop, a second crop was obtained of 45 g. (m. p. 278—281°). A sample, recrystallised from xylene (35 parts), had m. p. 280—283° (Found: C, 79·7; H, 3·45; N, 8·25. Calc. for $C_{23}H_{12}O_2N_2$: C, 79·3; H, 3·5; N, 8·0%).

Clemo and Perkin's Indolo(3′ : 2′-3 : 4)quinoline Synthesis.—Clemo and Perkin obtained two products from the reaction of toluene-*p*-sulphonanilide with β-chloropropionic acid, one the desired *N*-phenyl-*N*-toluene-*p*-sulphonyl-β-alanine and the other an unidentified product. Formation of the by-product was prevented by mixing the solutions at 20° and stirring at this temperature during 1 hr. before refluxing during 5 hr. Otherwise the details given by Clemo and Perkin are adequate.

Hope and Richter's Degradation of Ciba Yellow.—The degradation to the *N*-methyl-carboxylic acid is adequately described by the original authors but the decarboxylation proceeds much better as follows. The *N*-methyl-acid (4·7 g.) was refluxed in quinoline (15 c.c.) with copper bronze (1 g.) for 5 min. After cooling, the mixture was diluted with ether, filtered, and shaken with 2N-hydrochloric acid (60 c.c.). The solid was filtered off, washed with ether and water, and dried (yield, 3·1 g.; m. p. 168—170°). A further 0·5 g. was obtained from the ethereal layer of the filtrate. 4 G., recrystallised from ethyl acetate (100 c.c.; charcoal), gave 2 g. of m. p. 174—175° (Hope and Richter give m. p. 168°) (Found: C, 81·8; H, 5·0; N, 8·5; NMe, 8·7. Calc. for $C_{23}H_{16}ON_2$: C, 82·1; H, 4·8; N, 8·3; 1NMe, 8·6%).

Degradation of Ciba Yellow with Permanganate.—Ciba Yellow (30 g.) and 4N-sodium hydroxide (260 c.c.) were stirred and refluxed during 16 hr., then cooled and filtered from undissolved dye (0·4 g.). Potassium permanganate (197 g.) in cold water (3940 c.c.) was added. The mixture was stirred during 1 hr. and kept overnight. Ethanol (394 c.c.) was added to decompose the excess of permanganate, and solid carbon dioxide was added to slight alkalinity. The manganese dioxide was filtered off and well washed with water. The combined filtrate was acidified with hydrochloric acid. The solid was filtered off, washed with water, dried in a vacuum-desiccator (yield, 9 g.), and repeatedly digested with small portions of cold ethanol (70 c.c. in all; to remove a dark impurity), giving 3-o-*carboxyanilinophthalide*-3-*carboxy*-(o-

carboxyanilide) (XII) (5 g.), m. p. 224—225° (decomp.). The further purification of this compound by recrystallisation is attended by serious loss. It was considered sufficiently pure for the further degradative work, but for analysis 0·5 g. was refluxed during 30 min. with absolute ethanol (15 c.c.). After filtration colourless prisms slowly separated. These were collected and on drying broke down to a fine powder (0·06 g.), m. p. 226° (decomp.) (Found: C, 63·45; H, 3·75; N, 6·65. $C_{23}H_{16}O_7N_2$ requires C, 63·9; H, 3·7; N, 6·5%).

Further degradation, etc. (*a*) The product (XII) (0·33 g.) was refluxed during 5 hr. with 2N-hydrochloric acid (10 c.c.), filtered, and evaporated to dryness. The residue was washed with ether, dissolved in water (5 c.c.), and treated with sodium acetate (hydrated; 0·3 g.) in water (1 c.c.). After cooling in ice, anthranilic acid (0·05 g.), m. p. and mixed m. p. 140—142°, was collected.

(*b*) The product (XII) (0·743 g.) was dissolved in hot ethanol (100 c.c.). The solution was cooled, water (50 c.c.) was added, and the solution was titrated with 0·2006N-sodium hydroxide (pH meter) [Found: equiv., 227. $C_{21}H_{14}O_3N_2(CO_2H)_2$ requires equiv., 216].

(*c*) The anilide (XII) (0·700 g.) was refluxed during 3 hr. with N-sodium hydroxide (25 c.c.), then cooled. 1·023N-Hydrochloric acid (25 c.c.) was added. The solution and a control were titrated with sodium hydroxide (pH meter) (Found: equiv., 116. Four CO_2H, from hydrolysis of $C_{23}H_{16}O_7N_2$, require equiv., 108).

The solution remaining after titration was made up to a volume of 250 c.c. A portion (50 c.c.) was treated with 10N-hydrochloric acid (1 c.c.) and titrated with 0·0996N-sodium nitrite (Found: equiv., 228·5. Two NH_2 from hydrolysis of $C_{23}H_{16}O_7N_2$ require equiv., 216). As confirmation that the amine titrated was anthranilic acid, the diazotised amine was coupled with β-naphthol, yielding 0·16 g. of the azo-compound, m. p. 269° (decomp.) [lit., 272° (decomp.)].

The remaining 200 c.c. were acidified with 10N-hydrochloric acid (20 c.c.) and continuously extracted with ether overnight. The ethereal solution was filtered and evaporated. The residue was dissolved in hot water (20 c.c.). A solution of phenylhydrazine (1·1 c.c.) in hydrochloric acid (19 c.c.; 0·63N) was added. The solution was heated for 20 min. on the steam-bath and cooled in ice. The precipitated 1 : 2-dihydro-1-keto-2-phenylphthalazine-4-carboxylic acid (0·13 g.), washed with water and ethanol, had m. p. and mixed m. p. 208° (decomp.) (Found: C, 67·8; H, 4·1; N, 10·45. Calc. for $C_{15}H_{10}O_3N_2$: C, 67·7; H, 3·8; N, 10·5%).

(*d*) The product (XII) (0·5 g.), 60% aqueous hydrazine hydrate (1 c.c.), and water (2 c.c.) were heated on the steam-bath during 15 min., then cooled, diluted with water (3 c.c.), and acidified with hydrochloric acid. The 4-*phthalazone*-1-*carboxy*-(o-*carboxyanilide*) (IX) (0·3 g.) was filtered off, washed with water and dried. Recrystallised from acetic acid it had m. p. 333° (decomp.), undepressed in admixture with the synthetic product. The equivalent was determined by dissolution in pyridine and titration with sodium hydroxide (Found: C, 61·8; H, 3·9; N, 13·3%; equiv., 301. $C_{15}H_{10}O_2N_2{\cdot}CO_2H$ requires C, 62·1; H, 3·6; N, 13·6%; equiv., 309).

Condensation of Phthalonic Anhydride with Anthranilic Acid.—A mixture of phthalonic anhydride (2 g.), anthranilic acid (4 g.), and pyridine (5 c.c.) was kept at 95° during 30 min., with stirring at first to yield a clear solution. After cooling, the solution was added to 2N-hydrochloric acid (50 c.c.). The precipitated *phenylglyoxylanilide*-2 : 2′-*dicarboxylic acid* (X) (2·8 g.) soon crystallised. Recrystallised from anisole (14 c.c. per g.), washed with benzene, and dried at 100° *in vacuo*, it had m. p. 193—195° (decomp.) (Found: C, 61·8; H, 3·6; N, 4·4. $C_{16}H_{11}O_6N$ requires C, 61·35; H, 3·5; N, 4·5%).

Synthesis of 4-*Phthalazone*-1-*carboxy*-(o-*carboxyanilide*) (IX).—Phenylglyoxylanilide-2 : 2′-dicarboxylic acid (0·5 g.), water (2 c.c.), and 60% hydrazine hydrate (1 c.c.) were stirred for a few min., then heated on the steam-bath during 15 min. After cooling, the mixture was diluted with water and acidified with hydrochloric acid. The solid, when washed with water, dried, and recrystallised from acetic acid (200 c.c.) (yield 0·27 g.), had m. p. 333° (decomp.) (Found: C, 61·5; H, 3·5; N, 13·7%).

Reaction of Hope and Richter's Degradation Product with Hydrazine.—Hope and Richter's degradation product (XIII) (2·6 g.) in 2-ethoxyethanol (41·5 c.c.) was refluxed with 60% hydrazine hydrate (5·2 c.c.) during 6 hr. After cooling, the 6-o-*aminophenyl*-1′-*methyl*-3-*phenylindolo*(2′ : 3′-4 : 5)*pyridazine* (1·7 g.) was filtered off and washed with ethanol. Recrystallised from ethanol (150 c.c. per g.) it had m. p. 256—257° (Found: C, 78·6; H, 5·2; N, 16·2. $C_{23}H_{16}N_4$ requires C, 78·8; H, 5·2; N, 16·0%).

1′-*Methyl*-3 : 6-*diphenylindolo*(2′ : 3′-4 : 5)*pyridazine.*—(a) *Preparation by degradation.* 6-o-Aminophenyl-1′-methyl-3-phenylindolo(2′ : 3′-4 : 5)pyridazine (1 g.) was dissolved in 2N-hydrochloric acid (60 c.c.). The solution was cooled, filtered from a trace of insoluble matter, and

stirred with ice-cooling whilst 0·5N-sodium nitrite (5·5 c.c.) was added dropwise. Hypophosphorous acid (10 c.c. of 30%) was then added. The mixture was kept in ice during several hours and then at 20° overnight. The mixture then no longer exhibited a coupling reaction. The solid was filtered off, washed with water, dried, dissolved in pyridine (5 c.c.), and precipitated with water (50 c.c.). The *1'-methyl-3 : 6-diphenylindolo(2' : 3'-4 : 5)pyridazine* (0·25 g.) was filtered off, washed with water, and recrystallised from toluene, then having m. p. 229°, undepressed in admixture with the synthetic material and giving an identical *X*-ray powder photograph (Found : C, 82·2; H, 4·9; N, 12·5. $C_{23}H_{17}N_3$ requires C, 82·35; H, 5·1; N, 12·5%). A further 0·25 g. was obtained from the hydrochloric acid filtrate by basification and recrystallisation from ethanol.

(b) *Synthesis.* 1'-Methyl-2 : 3 : 6-triphenylindolo(2' : 3'-4 : 5)pyridazinium bromide (0·1 g. of the impure material A, below) was refluxed with hydrazine hydrate (1 c.c.; 60%) in 2-ethoxyethanol (10 c.c.) during 2 hr., kept at 20° overnight, and then evaporated on the steam-bath. The residue was dissolved in ethanol (2 c.c.), and the solution filtered from a trace of insoluble matter and cooled. 1'-Methyl-3 : 6-diphenylindolo(2' : 3'-4 : 5)pyridazine crystallised and had m. p. 229—230° (Found : C, 82·2; H, 5·1; N, 12·5%).

3-Benzoyl-1-methylindole-2-carboxylic Acid.—(*a*) Dry cadmium chloride (3·5 g.) was added to the Grignard reagent prepared from magnesium (0·55 g.), bromobenzene (2·75 c.c.), and ether (10 c.c.). The mixture was stirred and refluxed during 1 hr. by which time no phenylmagnesium bromide remained. A solution of 1-methylindole-2 : 3-dicarboxylic anhydride (2·8 g.) in hot benzene (100 c.c.) was added. The mixture was stirred and refluxed during 2 hr. Dilute hydrochloric acid was added, and the mixture was again stirred, refluxed for several min., and filtered. The organic layer was separated, washed with water, and extracted with sodium hydrogen carbonate solution. The extract was acidified with hydrochloric acid, and the gum was washed with water and crystallised from ethanol (15 c.c.), giving *3-benzoyl-1-methylindole-2-carboxylic acid* (0·8 g.), m. p. 163—164°. A further 1·9 g. of this compound were obtained by dilution of the filtrate with water. For analysis the first crop was recrystallised from ethanol (5 c.c.), forming very pale yellow plates, m. p. 165—166° (Found : C, 73·5; H, 4·8; N, 5·2. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7; N, 5·0%).

(*b*) A mixture of *N*-methyl-*N*-phenylhydrazine (8 c.c.) and ethyl benzoylpyruvate (15 g.) was heated on the steam-bath during 30 min., then at 100° under reduced pressure to remove water. Powdered zinc chloride (90 g.) was added and the whole kept in a bath at 85° whilst the mixture was stirred as well as possible. An exothermic reaction set in accompanied by frothing, the flask was removed from the bath, and the temperature of the mixture rose to 160°. After the temperature had fallen to 100°, water (250 c.c.) was added, and the mixture was acidified with hydrochloric acid and stirred at 100° to effect dissolution of the zinc chloride. After cooling in ice, the liquid was decanted, the sticky residue was dissolved in ethanol (80 c.c.), and 10N-sodium hydroxide was added (20 c.c.). The mixture was refluxed on the steam-bath during 30 min. The ethanol was removed and water (100 c.c.) added. The mixture was heated on the steam-bath, filtered hot, and cooled. Sodium chloride (10 g.) was added and the mixture stirred to effect dissolution of the sodium chloride. The solid was filtered off, washed with brine, and dissolved in water (100 c.c.). This solution was added to 10N-hydrochloric acid (10 c.c.) containing some ice and a small seed-crystal. The precipitated solid (8·7 g.), recrystallised from 60% ethanol (60 c.c.; charcoal), had m. p. 165—166° (6·5 g.), undepressed in admixture with the product prepared as in (*a*).

2 : 3-Dihydro-3-keto-1'-methyl-2 : 6-diphenylindolo(2' : 3'-4 : 5)pyridazine (XX).—Phenylhydrazine (5 c.c.) and 3-benzoyl-1-methylindole-2-carboxylic acid (10 g.) were heated in ethanol (30 c.c.) during 80 min. After cooling, the *indolopyridazine* was filtered off, washed with ethanol, and dried (11·3 g.). Recrystallised from benzene it had m. p. 157° (Found : C, 78·4; H, 4·7; N, 12·1. $C_{23}H_{17}ON_3$ requires C, 78·6; H, 4·9; N, 12·0%).

1'-Methyl-2 : 3 : 6-triphenylindolo(2' : 3'-4 : 5)pyridazinium Bromide (XXI).—The Grignard reagent prepared from magnesium (0·41 g.), bromobenzene (2·1 c.c.), and ether (10 c.c.) was added with shaking to a hot solution of the indolopyridazone (XX) (5·7 g.) in benzene (100 c.c.). After 1 min. water and dilute hydrochloric acid were added. The solid collected after cooling was mainly starting material (5 g.), m. p. and mixed m. p. 155—157°. A portion (4 g.) of this material was boiled with dry benzene (100 c.c.), and the solid was filtered off hot, washed with warm benzene and dried (yield, 0·21 g.; m. p. 295—297°). 0·1 G. of this product, when recrystallised from pyridine–benzene, had m. p. *ca.* 310° (A; see above). This gave analyses for the expected quaternary bromide containing about 15% of the quaternary chloride (Found : C, 72·1; H, 5·0; N, 8·7; Br, 14·4. Calc. for $C_{29}H_{22}N_3Br_{0\cdot85}Cl_{0\cdot15}$: C, 71·7; H, 4·6; N, 8·7;

Br, 14·0%). The hot benzene filtrate was further treated with the Grignard reagent prepared from magnesium (0·29 g.), bromobenzene (1·5 c.c.), and ether (7 c.c.). The ether was distilled off and the benzene solution was refluxed during 45 min., and kept at 20° overnight. Water and dilute hydrochloric acid were added. The solid was filtered off, washed with benzene and water, and dried, giving material (3·1 g.) of m. p. 149—151° undepressed in admixture with the starting material. This product was boiled with benzene (100 c.c.); the solid, filtered off hot, washed with hot benzene, and dried, had m. p. 294—297° (1·2 g.).

1 : 4-*Diphenylphthalazine*.—Reaction of 1 : 2-dihydro-1-keto-2 : 4-diphenylphthalazine with phenylmagnesium bromide and conversion of the resulting quaternary bromide into 1 : 4-diphenylphthalazine by hydrazine were carried out substantially as described for the indolopyridazine analogue. The resulting 1 : 4-diphenylphthalazine melted at 193—194° undepressed in admixture with an authentic sample.

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388. *Intramolecular Acylation. Part III.* The Preparation and Ring Closure of the α-Methoxyphenylglutaric Acids.*

By D. H. HEY and K. A. NAGDY.

Methods are described for the preparation of α-*o*-, α-*m*-, and α-*p*-methoxyphenylglutaric acid, and a study has been made of the action of cyclising agents on these acids and their acid chlorides. In this manner α-*m*-methoxyphenylglutaric acid and its acid chloride were converted successively into 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic, 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic, and 7-methoxy-1-naphthoic acid. α-*p*-Methoxyphenylglutaryl chloride was similarly converted into 1 : 2 : 3 : 4-tetrahydro-4-keto-6-methoxy-1-naphthoic acid. Further evidence is produced of the deactivating influence of the nearer carboxyl group in the Friedel–Crafts-type cyclisation of substituted dicarboxylic acids.

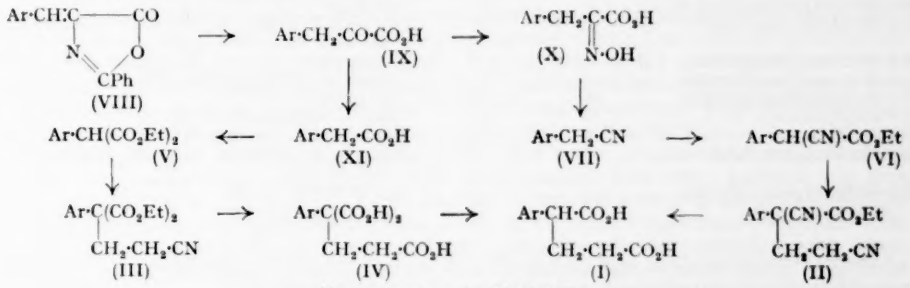
IN a previous communication (*J.*, 1950, 1683) a general method for the preparation of α-substituted glutaric acids was described and subsequently (Part II *) a number of these acids were converted by conventional methods into monocarboxylic acids of cyclic ketones. The present communication describes an extension of this work with the three α-methoxyphenylglutaric acids. Experimental work with the β-methoxyphenylglutaric acids was reported in Part I (*J.*, 1949, 3177).

The three isomeric α-methoxyphenylglutaric acids (I) were prepared by the general method referred to above, which involves cyanoethylation of an appropriate malonic or cyanoacetic ester followed by hydrolysis and decarboxylation. Whereas in the unsubstituted series hydrolysis was effected with 48% hydrobromic acid, this reagent, which caused partial demethylation in the present series of compounds, was replaced by aqueous-alcoholic potassium hydroxide. With the cyanoethylated cyanoacetic esters (II) this reagent brought about both hydrolysis and decarboxylation, whereas with the cyanoethylated malonic esters (III) under similar conditions the tricarboxylic acids (IV) were formed, which were subsequently decarboxylated at 180—185°. Similar results were noted when ethyl *m*-methoxyphenylmalonate (V; Ar = *m*-MeO·C_6H_4) and ethyl α-cyano-α-*m*-methoxyphenylacetate (VI; Ar = *m*-MeO·C_6H_4) were subjected to hydrolysis with aqueous-alcoholic potassium hydroxide, the former giving *m*-methoxyphenylmalonic acid and the latter *m*-methoxyphenylacetic acid. These results can be attributed to the greater electron-attracting power of the cyano-group compared with that of the carbethoxy-group, which facilitates the removal of elements of carbon dioxide from the carbon atom to which it is attached.

The three isomeric cyanoacetic esters (VI; Ar = *o*-, *m*-, and *p*-MeO·C_6H_4) were prepared in moderate yield by the condensation of the appropriate methoxybenzyl cyanide

* Part II, *J.*, 1950, 2874.

(VII) with ethyl carbonate in presence of sodium (cf. Niederl, Roth, and Plentl, *J. Amer. Chem. Soc.*, 1937, **59**, 1901; Niederl and Roth, *ibid.*, 1938, **60**, 2140; Wallingford, Jones, and Homeyer, *ibid.*, 1942, **64**, 576). The methoxybenzyl cyanides (VII) were prepared in good yield by the condensation of the methoxybenzaldehyde with hippuric acid, hydrolysis of the resulting azlactone (VIII) with 10% aqueous sodium hydroxide, conversion of the pyruvic acid (IX) into its oxime (X), and subsequent dehydration and decarboxylation (cf. Carter, " Organic Reactions," Vol. III, p. 198). For the preparation of ethyl *m*-methoxyphenylmalonate the method of Wallingford, Homeyer, and Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 2056) was used, in which the methoxyphenylacetic ester is condensed with an excess of ethyl carbonate in the presence of sodium ethoxide, but this method failed with the *para*-isomer and was only partly successful with the *ortho*-isomer. The methoxyphenylacetic esters were prepared by the esterification of the acids (XI) obtained by the oxidation of the corresponding pyruvic acids (IX) with alkaline hydrogen peroxide (cf. Carter, *loc. cit.*). Whereas the cyanoethylation of the α-cyano-α-methoxyphenylacetates (VI) with subsequent hydrolysis and decarboxylation gave the α-methoxyphenylglutaric acids in yields of more than 70% with all three isomers, the alternative route by means of the methoxyphenylmalonate (V) gave yields of only 16% in the *ortho*-series and of 18% in the *meta*-series.



(Ar = *o*-, *m*-, and *p*-MeO·C$_6$H$_4$)

Preliminary attempts to cyanoethylate the three α-methoxybenzylmalonic esters with acrylonitrile at 30—35° in presence of methanolic potassium hydroxide failed. These esters were prepared by the condensation of the methoxybenzaldehyde with ethyl malonate in presence of piperidine, followed by reduction of the resulting methoxybenzylidenemalonic ester with Raney nickel.

In order to obtain further information on the influence of both the nuclear methoxyl group and the second carboxyl group on the cyclisation process by means of which ketonic acids are formed, the three isomeric α-methoxyphenylglutaric acids or their acid chlorides were submitted to the action of the conventional cyclising agents. Cyclodehydration occurred readily with α-*m*-methoxyphenylglutaric acid with the common cyclising reagents (anhydrous hydrogen fluoride, 95% sulphuric acid, polyphosphoric acid, stannic chloride), but no keto-acids could be obtained from the *o*- or *p*-acid. Cyclodehydrohalogenation was effective with both stannic chloride and aluminium chloride in the case of α-*m*-methoxyphenylglutaryl chloride, but the yields were low. α-*p*-Methoxyphenylglutaryl chloride was also cyclised with aluminium chloride in nitrobenzene solution at 0°, but only in 10% yield. Ring closure could not be effected with the acid chloride of α-*o*-methoxyphenylgutaric acid. These results are in agreement with expectation because in α-*m*-methoxyphenylglutaric acid the activating effect of the methoxyl group far outweighs the deactivating effect of the carboxyl group, whereas with the *ortho*- and *para*-acids this situation does not exist. Attention was directed to the deactivating influence of a carboxyl group attached to the carbon atom adjacent to the aromatic nucleus by Badger, Campbell, and Cook (*J.*, 1949, 1084) in the cyclisation of αβ-diphenylglutaric acid, and a further example seemed to be provided by the cyclisation of α-phenylglutaric acid to give 1 : 2 : 3 : 4-tetrahydro-4-keto-1-naphthoic acid (Ansell and Hey, *J.*, 1950, 2874). α-Arylglutaric acids may be regarded as carboxy-

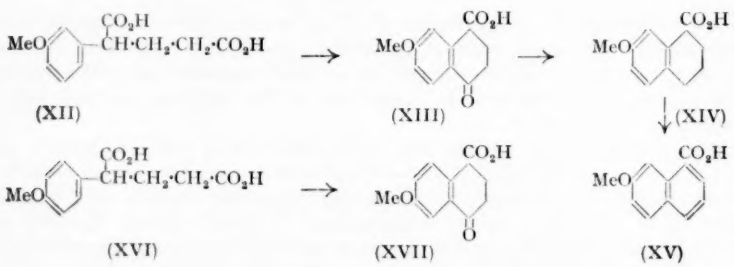
derivatives of γ-arylbutyric acids, and β-arylglutaric acids as carboxymethyl derivatives of β-arylpropionic acids, and a comparison of the yields obtained on cyclodehydration with anhydrous hydrogen fluoride in the two series clearly shows the marked deactivating influence of the second and nearer acidic group (see Table), which is probably present as $Ar{\cdot}CH{\cdot}CO^+$ in the reacting system.

Cyclisation of α-*m*-methoxyphenylglutaric acid (XII) or its acid chloride can give either 1 : 2 : 3 : 4-tetrahydro-4-keto-5- or -7-methoxy-1-naphthoic acid, but the identity of the product as the latter, *viz.*, (XIII), was confirmed by means of Clemmensen reduction to the known 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic acid (XIV), which in turn was dehydrogenated to 7-methoxy-1-naphthoic acid, m. p. 167—168° (XV). Had cyclisation taken place at the *ortho*-position with reference to the methoxyl group this sequence of reactions would have given 5-methoxy-1-naphthoic acid, m. p. 229°. The cyclisation of

Acid	Size of ring	Yield of cyclised product (%)	Reference
γ-Phenylbutyric	6	92	Fieser & Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272.
α-Phenylglutaric	6	17	Ansell & Hey, *J.*, 1950, 2874.
γ-*m*-Methoxyphenylbutyric	6	85—90 *	Peak & Robinson, *J.*, 1937, 1581.
α-*m*-Methoxyphenylglutaric	6	87	This paper.
γ-*p*-Methoxyphenylbutyric	6	61·5	Campbell & Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 928.
α-*p*-Methoxyphenylglutaric	6	0	This paper.
γ-*o*-Methoxyphenylbutyric	6	55 †	Lockett & Short, *J.*, 1939, 787.
α-*o*-Methoxyphenylglutaric	6	0	This paper.
β-Phenylpropionic	5	73	Fieser & Hershberg, *loc. cit.*
β-Phenylglutaric	5	10·5	Hey & Kohn, *J.*, 1949, 3177.
β-*p*-Methoxyphenylpropionic	5	3	Johnson & Shelberg, "Organic Reactions," Vol. II, 120.
β-*p*-Methoxyphenylglutaric	5	0	Hey & Kohn, *loc. cit.*

* With $SnCl_4$. † With $POCl_3$.

α-*p*-methoxyphenylglutaric acid (XVI) offers no ambiguity and the 6-methoxy acid (XVII) was obtained and characterised as the oxime and semicarbazone.



Experimental

Preparation of the Acids.

α-o-*Methoxyphenylglutaric Acid.*—(*a*) *o*-Methoxybenzaldehyde was converted into *o*-methoxybenzyl alcohol in 72% yield by Davidson and Bogert's method (*J. Amer. Chem. Soc.*, 1935, **57**, 905) and thence into the chloride and cyanide, as described by Niederl and Roth (*loc. cit.*). In an alternative method the azlactone, m. p. 163—166° (from ethyl acetate), was prepared in 70% yield from *o*-methoxybenzaldehyde and hippuric acid by the method of Bergel, Haworth, Morrison, and Rinderknecht (*J.*, 1944, 263), who reported m. p. 154—156° from alcohol; hydrolysis of the azlactone with 10% aqueous sodium hydroxide gave *o*-methoxyphenylpyruvic acid, which was converted into the oxime and treated with acetic anhydride (cf. Niederl and Ziering, *J. Amer. Chem. Soc.*, 1942, **64**, 885) to give *o*-methoxybenzyl cyanide in 36% yield (calc. on *o*-methoxybenzaldehyde). Condensation of *o*-methoxybenzyl cyanide with ethyl carbonate, as described by Niederl and Roth (*loc. cit.*) but with two molecular proportions of ethyl

carbonate, gave ethyl α-cyano-α-*o*-methoxyphenylacetate in 32% yield. To a stirred solution of this ester (3·2 g.) and 30% methanolic potassium hydroxide (1 c.c.) in *tert.*-butyl alcohol (12 c.c.) was added pure acrylonitrile (1 c.c.). The mixture was kept at 30—35° for 3 hr., then diluted with water, neutralised with dilute hydrochloric acid, and extracted with ether. After being washed with water and dried ($MgSO_4$), the extract was heated on the water-bath under reduced pressure. The residual ethyl αγ-dicyano-α-*o*-methoxyphenylbutyrate (4 g.) was boiled under reflux for 6 hr. with a solution of potassium hydroxide (4 g.) in ethyl alcohol (4 c.c.) and water (4 c.c.). The alcohol was removed by distillation and the solution was cooled, diluted with water, washed with ether, acidified, and then extracted with ether. Evaporation of the dried extract left a solid residue, m. p. 162—164°. Recrystallisation from ethylene chloride gave α-o-*methoxyphenylglutaric acid* (2·7 g.), m. p. 164—166° (Found: C, 60·9; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

(*b*) To an ice-cold solution of *o*-methoxyphenylpyruvic acid [from *o*-methoxybenzaldehyde (100 g.) as outlined in method (*a*)] in 10% aqueous sodium hydroxide (300 c.c.) was added hydrogen peroxide (10-vols.; 500 c.c.) at intervals. After being kept at 0° overnight the solution was acidified and *o*-methoxyphenylacetic acid (44 g.), m. p. 120—123°, separated (cf. Robinson and Zaki, *J.*, 1927, 2411), which was converted into the ethyl ester, b. p. 150°/18 mm., in 80% yield by 5 hr.' boiling under reflux with absolute ethyl alcohol (300 c.c.) and concentrated sulphuric acid (10 c.c.). Ethyl *o*-methoxyphenylacetate (19·4 g.), dry ethyl carbonate (100 c.c.), and sodium ethoxide (from 2·45 g. of sodium) by the method of Wallingford, Homeyer, and Jones (*loc. cit.*) gave crude ethyl *o*-methoxyphenylmalonate (7·2 g.; b. p. 125—140°/0·8 mm.), which was dissolved in *tert.*-butyl alcohol (30 c.c.) to which 30% methanolic potassium hydroxide (2 c.c.) and acrylonitrile (1·8 c.c.) were added. After being stirred for 3 hr. at 30—35° the mixture was diluted with water, neutralised with dilute hydrochloric acid, and extracted with ether. Evaporation of the dried extract gave crude ethyl α-2-cyanoethyl-α-o-methoxyphenylmalonate (8 g.), which was boiled under reflux for 6 hr. with a solution of potassium hydroxide (8 g.) in ethyl alcohol (8 c.c.) and water (8 c.c.). After removal of the alcohol the solution was cooled, diluted with water, washed with ether, acidified, and then extracted with ether. Evaporation of the ethereal extract left α-carboxy-α-*o*-methoxyphenylglutaric acid as an oil, which was decarboxylated at 180—185° (bath-temp.) for 1 hr. The cooled product was boiled with water for 15 min., cooled, and extracted with ether. Evaporation of the dried extract gave α-*o*-methoxyphenylglutaric acid, which after three crystallisations from ethylene chloride had m. p. 164—166° (1 g.) alone and on admixture with the acid prepared by method (*a*).

α-m-*Methoxyphenylglutaric Acid.*—(*a*) The azlactone (m. p. 108°; 50 g.) prepared from *m*-methoxybenzaldehyde and hippuric acid (Pschorr, *Annalen*, **1912**, **391**, 44) gave *m*-methoxyphenylpyruvic acid (20 g.; m. p. 150°), which was converted successively into the oxime (20 g.; m. p. 140°) and *m*-methoxybenzyl cyanide (7 g.; b. p. 100°/4·6 × 10^{-3} mm.). Condensation of the cyanide (6·3 g.) with dry ethyl carbonate (15 c.c.) and powdered sodium (0·9 g.) in dry ether (20 c.c.) by Niederl and Roth's method (*loc. cit.*) gave ethyl α-cyano-α-*m*-methoxyphenylacetate (4·9 g.; b. p. 120—125°/5 × 10^{-3} mm.). Hydrolysis of a portion of this ester with boiling aqueous-alcoholic potassium hydroxide gave *m*-methoxyphenylacetic acid, m. p. 68—69°. Ethyl α-cyano-α-*m*-methoxyphenylacetate (3·7 g.) and acrylonitrile (1·2 c.c.) by the method described above for the corresponding *o*-isomeride gave ethyl αγ-dicyano-α-*m*-methoxyphenylbutyrate as a viscous oil (4·6 g.), and on hydrolysis α-m-*methoxyphenylglutaric acid* (2·9 g.) in plates, m. p. 121—122° after crystallisation from ether–light petroleum (b. p. 40—60°) (Found: C, 60·5; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

(*b*) The azlactone (50 g.) from *m*-methoxybenzaldehyde was converted into *m*-methoxyphenylpyruvic acid (20 g.) and then into *m*-methoxyphenylacetic acid (15·5 g.), m. p. 68—69°, and its ethyl ester (14·8 g.), b. p. 90°/1·27 × 10^{-2} mm. as described in the previous example. By the method of Wallingford, Homeyer, and Jones (*loc. cit.*), ethyl *m*-methoxyphenylacetate (26 g.) and dry ethyl carbonate (110 c.c.) in the presence of sodium ethoxide (from 3·2 g. of sodium) gave ethyl *m*-methoxyphenylmalonate (23·5 g.), b. p. 128—132°/0·35 mm. A portion on hydrolysis with aqueous alcoholic potassium hydroxide gave m-*methoxyphenylmalonic acid* in prisms, m. p. 116—117° (decomp.) (from chloroform) (Found: C, 57·0; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). By the method described above ethyl *m*-methoxyphenylmalonate (13·3 g.), 30% methanolic potassium hydroxide (2 c.c.), and acrylonitrile (3·3 c.c.) in *tert.*-butyl alcohol (50 c.c.) at 30—35° for 3 hr. gave ethyl α-2-cyanoethyl-α-*m*-methoxyphenylmalonate (15·8 g.), which was hydrolysed as above to α-carboxy-α-*m*-methoxyphenylglutaric acid, an oil, which in turn was decarboxylated at 180—185° for 1 hr. α-*m*-Methoxyphenylglutaric acid (2·1 g.) was obtained in

plates, m. p. 121—122°, from ether–light petroleum (b. p. 40—60°) alone and on admixture with the acid prepared by method (*a*).

α-p-*Methoxyphenylglutaric Acid*.—The azlactone (m. p. 156—158°; 50 g.), prepared in 80% yield from *p*-methoxybenzaldehyde and hippuric acid (Dakin, *J. Biol. Chem.*, 1910, **8**, 17), was converted successively into *p*-methoxyphenylpyruvic acid, m. p. 184° (23 g.), its oxime, m. p. 159° (22 g.), and *p*-methoxybenzyl cyanide, b. p. 92°/1·5 × 10^{-2} mm. (11 g.), identical with a specimen prepared by the methylation of *p*-hydroxybenzyl cyanide (Meisenheimer and Weibezahn, *Ber.*, 1921, **54**, 3200). The *p*-methoxybenzyl cyanide (13·2 g.), dry ethyl carbonate (12 c.c.), and sodium (2·1 g.) in dry ether (30 c.c.), by the method of Niederl, Roth, and Plentl (*loc. cit.*), gave ethyl α-cyano-α-*p*-methoxyphenylacetate, b. p. 132—135°/8·16 × 10^{-3} mm. (10·7 g.). By the method outlined above this ester (9·5 g.) with 30% methanolic potassium hydroxide (2 c.c.) and acrylonitrile (2·9 c.c.) in *tert.*-butyl alcohol (25 c.c.) at 30—35° gave ethyl αγ-dicyano-α-*p*-methoxyphenylbutyrate (11·6 g.) as a viscous oil, which after hydrolysis with aqueous-alcoholic potassium hydroxide as above gave α-p-*methoxyphenylglutaric acid* (8 g.), m. p. 137—138°, in needles from ether–light petroleum (b. p. 40—60°) (Found: C, 60·8; H, 6·0. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%).

o-, m-, and p-*Methoxybenzylmalonic Acids*.—These acids were prepared from dry ethyl malonate (12 c.c.), the appropriate methoxybenzaldehyde (10 g.), and piperidine (2 c.c.) by setting the mixture aside for 2 days and then boiling it under reflux for 12 hr. The cold mixture was diluted with ether (100 c.c.), washed successively with water, dilute sulphuric acid, and water, dried ($MgSO_4$), and distilled under reduced pressure. The resulting methoxybenzylidenemalonic esters were hydrogenated in alcohol at room temperature over Raney nickel and then hydrolysed to the methoxybenzylmalonic acids with aqueous-alcoholic potassium hydroxide. The following compounds were obtained: *ethyl* o-*methoxybenzylidenemalonate*, needles, m. p. 49·5—50·5° (from alcohol) (Found: C, 64·5; H, 6·4. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·4%); o-*methoxybenzylmalonic acid*, m. p. 140° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 59·1; H, 5·3. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%); ethyl *m*-methoxybenzylidenemalonate, b. p. 160°/3 × 10^{-3} mm.; m-*methoxybenzylmalonic acid*, m. p. 100—102° [from ether-light petroleum (b. p. 40—60°)] (Found: C, 58·7; H, 5·5%); ethyl *p*-methoxybenzylidenemalonate, m. p. 38—40° (cf. Marckwald, *Ber.*, 1898, **31**, 2594); ethyl *p*-methoxybenzylmalonate, b. p. 122—123°/6·85 × 10^{-3} mm. (cf. Bowden and Adkins, *J. Amer. Chem. Soc.*, 1940, **62**, 2422); and p-*methoxybenzylmalonic acid*, m. p. 119—120° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 59·4; H, 5·4%).

Ring Closure Experiments.

(a) *Cyclodehydration*.—(i) A mixture of anhydrous hydrogen fluoride (*ca.* 50 c.c.) and α-*m*-methoxyphenylglutaric acid (0·5 g.) in a "Polythene" beaker was left for 24 hr. in the open under shelter, after which ice-cold water was added. The separated solid was extracted with ether and the ethereal extract washed with aqueous sodium carbonate. The alkaline extract was acidified and extracted with ether. Evaporation of the solvent from the dried extract left 1 : 2 : 3 : 4-*tetrahydro*-4-*keto*-7-*methoxy*-1-*naphthoic acid* (0·4 g.), long needles, m. p. 155° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 65·2; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·45%). The *semicarbazone* separated from alcohol in long needles, m. p. 221—222° (Found: C, 56·9; H, 5·6. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·4%). A mixture of amalgamated zinc turnings (2 g.), water (2 c.c.), concentrated hydrochloric acid (3 c.c.), toluene (5 c.c.), acetic acid (0·2 c.c.), and the keto-acid (0·4 g.) was boiled under reflux for 30 hr., during which a further quantity of hydrochloric acid (4 c.c.) was added in portions. The toluene layer was then collected and when cold 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-naphthoic acid (0·2 g.) gradually separated in colourless prisms, m. p. 137—138° (cf. Fieser and Holmes, *J. Amer. Chem. Soc.*, 1936, **58**, 2319). When this acid (0·15 g.) was heated at 220—240° for ½ hr. with sulphur (0·5 g.) dehydrogenation was effected, and digestion of the cold mixture with aqueous sodium carbonate extracted the acid. The alkaline solution was acidified and extracted with ether. Evaporation of the dried extract gave 7-methoxy-1-naphthoic acid, which after crystallisation from dilute alcohol and then twice from hexane was obtained in needles, m. p. 166—167° (cf. Davies, Heilbron, and Irving, *J.*, 1932, 2715, and Fieser and Holmes, *loc. cit.*).

(ii—iv) 1 : 2 : 3 : 4-Tetrahydro-1-keto-7-methoxy-1-naphthoic acid, m. p. 154°, was obtained in yields of 0·10 g., 0·11 g., and 0·11 g. respectively when α-*m*-methoxyphenylglutaric acid (0·2 g.) was (*a*) stirred with 95% sulphuric acid (2 c.c.) for 1 hr. at 0° and a second hour at 20°, (*b*) stirred at 100° for 15 min. with polyphosphoric acid (2 c.c.), and (*c*) stirred at 120° for 20 min. with stannic chloride (2 c.c.).

Cyclodehydration failed with both α-*o*- and α-*p*-methoxyphenylglutaric acid and (*a*) anhydrous hydrogen fluoride, (*b*) 85% and 95% sulphuric acid at 0°, (*c*) polyphosphoric acid at 100°, and (*d*) stannic chloride at 120°, and with α-*m*-methoxyphenylglutaric acid and cold 85% sulphuric acid.

(b) *Cyclohydrohalogenation.*—(i) A mixture of α-*m*-methoxyphenylglutaric acid (0·1 g.) and phosphorus pentachloride (0·2 g.) in dry benzene (5 c.c.) was kept at room temperature for 1 hr. and then boiled for 5 min. on the water-bath. After the removal of benzene, phosphorus oxychloride, and phosphorus pentachloride under reduced pressure the residual α-*m*-methoxyphenylglutaryl chloride was dissolved in benzene (3 c.c.) and cooled, and a solution of stannic chloride (0·2 c.c.) in benzene (2 c.c.) added. The mixture was shaken, kept at 0° for 15 min., and then decomposed with ice and hydrochloric acid. The product was extracted with ether, and the extract was washed successively with dilute hydrochloric acid, water, and aqueous sodium carbonate. The alkaline solution was acidified and extracted with ether, evaporation of which left an oil, which was heated in ethyl alcohol (5 c.c.) at 70° for 1 hr. with a solution of semicarbazide hydrochloride (0·1 g.) in water (1 c.c.) and pyridine (0·1 c.c.). Next morning the semicarbazone (20 mg.), m. p. 221—222°, of 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic acid separated in long needles. Hydrolysis with dilute hydrochloric acid gave the free acid (13 mg.), which separated from ether–light petroleum (b. p. 40—60°) in long needles, m. p. 155° alone and on admixture with the compound prepared from α-*m*-methoxyphenylglutaric acid and anhydrous hydrogen fluoride.

(ii) Anhydrous aluminium chloride (0·4 g.) was added to a solution of α-*m*-methoxyphenylglutaryl chloride (from 0·3 g. acid) in nitrobenzene (5 c.c.) at room temperature. After 15 min. the mixture was stirred at 60—70° for 15 min. and then decomposed with ice and hydrochloric acid. The nitrobenzene was removed with steam, and the residue was extracted with ether. Working up as usual and crystallisation (charcoal) from ether–light petroleum (b. p. 40—60°) gave 1 : 2 : 3 : 4-tetrahydro-4-keto-7-methoxy-1-naphthoic acid (85 mg.) as needles, m. p. 155°, identical with the product obtained by method (i).

(iii) Anhydrous aluminium chloride (1·3 g.) was added to a solution of α-*p*-methoxyphenylglutaryl chloride (from 1·0 g. of acid) in nitrobenzene (15 c.c.) at 0°. After ½ hr. the mixture was added to ice and concentrated hydrochloric acid, and treated as in the preceding example. Purification of the product with charcoal and two crystallisations from ether–light petroleum (b. p. 40—60°) gave 1 : 2 : 3 : 4-*tetrahydro*-4-*keto*-6-*methoxy*-1-*naphthoic acid* (90 mg.) in plates, m. p. 115° (Found: C, 65·5; H, 5·4. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·45%). The *oxime* separated from ethylene chloride in platelets, m. p. 202° (Found: N, 5·5. $C_{12}H_{13}O_4N$ requires N, 5·95%), and the *semicarbazone* from alcohol in needles, m. p. 255° (Found: N, 14·0. $C_{13}H_{15}O_4N_3$ requires N, 15·1%).

Cyclodehydrohalogenation failed with α-*o*-methoxyphenylglutaryl chloride and (*a*) stannic chloride in benzene, (*b*) aluminium chloride in carbon disulphide, and (*c*) aluminium chloride in nitrobenzene, with α-*m*-methoxyphenylglutaryl chloride and aluminium chloride in carbon disulphide, and with α-*p*-methoxyphenylglutaryl chloride and (*a*) stannic chloride in benzene and (*b*) aluminium chloride in carbon disulphide.

One of us (K. A. N.) expresses his thanks to the Egyptian Ministry of Education for the award of a grant.

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389. *The Alleged "Carbazoacridines."*

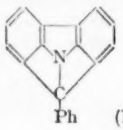
By R. M. Acheson and B. F. Sansom.

Bizzarri's supposed "carbazoacridines" are shown to be, probably, impure 3-acylcarbazoles.

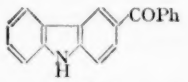
Bizzarri (*Gazzetta*, 1890, **20**, 407; 1891, **21**, 158, 351; 1892, **23**, 1) claimed to have obtained methyl- and phenyl-"carbazoacridine" (I) by heating *N*-acetyl- and *N*-benzoylcarbazole, or carbazole and the free acids, with zinc chloride, and from the acid amides and carbazole in the presence of phosphoric oxide. The only other reference to "carbazoacridines" in the literature is that of Ilberg and Reichel (*Ber.*, 1943, **76**, 1108) who mention the reaction of the phenyl derivative with tellurium tetrachloride.

The structure (I) suggested is impossible on steric grounds, and as the rearrangement of *N*-acylcarbazoles with aluminium chloride gives 3-acylcarbazoles (Plant and Tomlinson, *J.*, 1932, 2188; Plant, Rogers, and Williams, *J.*, 1935, 741) it was thought that the "carbazoacridines" might be compounds of the latter type. However the melting points of the "carbazoacridines" did not coincide with those of the known acetyl- or benzoylcarbazoles and the analytical data did not agree with such a formulation. Another possibility was that they were acridines formed either by a ring expansion or from diphenylamine present in the carbazole as an impurity. Bizzarri's analytical data and m. p. (186°) for "phenylcarbazoacridine," and the m. p. (172°) and non-basicity of its "dihydroderivative" corresponded well with the properties of 9-phenylacridine (m. p. 184°) and 9-phenylacridan (m. p. 170°). His claim that "phenylcarbazoacridine methiodide" decomposed, when heated, to methyl iodide and the original "carbazoacridine" supported this view.

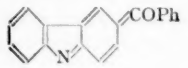
One of Bizzarri's methods was therefore reinvestigated. We should mention that Dr. S. G. P. Plant isolated carbazole and 3-benzoylcarbazole after heating *N*-benzoylcarbazole with zinc chloride for 4 hr. at 130—50° (unpublished work). Benzoic acid, carbazole, and zinc chloride were heated according to Bizzarri's method; the product, after one crystallisation, had the properties ascribed to "phenylcarbazoacridine." Further recrystallisation, however, gave only 3-benzoylcarbazole (II). Chromatography of the crude product or of *N*-benzoylcarbazole gave carbazole and benzoic acid. Diphenylamine, benzoic acid, and zinc chloride gave no 9-phenylacridine under Bizzarri's conditions.



(I)



(II)



(III)

3-Benzoylcarbazole was little affected by zinc and acetic acid, used by Bizzarri for the reduction of "phenylcarbazoacridine" to its "dihydro-derivative," but with hydrogen over Raney nickel gave 3-benzylcarbazole. A mixture of the ketone and 3-benzylcarbazole was obtained if the hydrogenation was stopped before completion. This is a most unusual result as such reductions usually give alcohols; dehydration of the alcohol to (III) followed by further reduction might account for the result, and such a dehydration would be acid-catalysed; addition of alkali to the hydrogenation mixture did not however affect the course of the reaction.

Bizzarri also stated that potassium permanganate oxidised "phenylcarbazoacridine" to "1:8-carbonylcarbazole," m. p. 177—179°, and described nitroso- and acetyl derivatives. The substance may be impure carbazole-3-carboxylic acid; this has m. p. 267—268° (Plant and Williams, *J.*, 1934, 1142).

A repetition of Bizzarri's "methylcarbazoacridine" preparation from acetic acid, etc., gave a product from which nothing crystalline could be isolated. Treatment with 2:4-di-

nitrophenylhydrazine in ethanolic hydrogen chloride gave 3-acetylcarbazole 2 : 4-dinitrophenylhydrazone.

Experimental

3-Benzoylcarbazole.—Carbazole (10·0 g.), benzoic acid (7·5 g.), and anhydrous zinc chloride (25 g.) were heated in an oil-bath at 150—170° for 5 hr. No crystalline product could be isolated if the temperature was kept at 205°. The very viscous melt was cooled, dissolved in boiling ethanol, and treated with aqueous ammonia (75 c.c.; *d* 0·880), followed by water until no more dark fawn-coloured precipitate (25 g.) was formed. Nothing could be extracted from this solid by dilute alkali.

A portion, after one recrystallisation from ethanol (charcoal) containing ammonia gave a heterogeneous solid of which the yellow crystalline constituent became green and sintered at 130—150°, had m. p. 180—190°, and corresponded to Bizzarri's "phenylcarbazoacridine" of m. p. 186°. Further recrystallisation of the whole solid from ethanol gave 3-benzoylcarbazole (10—15%) as yellow rhombs, m. p. 206° (Found: C, 83·6; H, 4·9; N, 4·9. Calc. for $C_{19}H_{13}ON$: C, 84·1; H, 4·8; N, 5·2%) alone or mixed with an authentic specimen. The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid as a microcrystalline red powder, m. p. 305° (decomp.) (Found: C, 66·6; H, 3·7. $C_{25}H_{17}O_4N_5$ requires C, 66·6; H, 3·8%). The original condensation gave 63% of 3-benzoylcarbazole, estimated in the crude product by this derivative.

Chromatography of the crude product in benzene on alumina gave carbazole, m. p. 243° alone or mixed with an authentic specimen, and elution with benzene–ether (1 : 1) gave benzoic acid. *N*-Benzoylcarbazole also gave carbazole and benzoic acid on a similar column.

3-Acetylcarbazole.—Carbazole (8·0 g.), acetic acid (3·5 g.), and zinc chloride (12 g.) were heated in a sealed tube to 150° for 5 hr. The resulting black tar was dissolved in ethanol and filtered into aqueous ammonia; a fawn-coloured precipitate (2·9 g.) was obtained. Extraction of this precipitate with benzene gave a small quantity of carbazole. The insoluble material gave a red 2 : 4-dinitrophenylhydrazone which after crystallisation from acetic acid and chromatographic purification had m. p. 318—319° (decomp.) (Found: C, 61·7; H, 4·1. $C_{20}H_{15}O_4N_5$ requires C, 61·7; H, 3·9%), unchanged when mixed with authentic 3-*acetylcarbazole* 2 : 4-*dinitrophenylhydrazone* (crystallised from acetic acid), m. p. 320° (decomp.) (Found: C, 61·9; H, 3·8%). The infra-red absorption spectra of the compounds in paraffin paste were identical, and showed the maxima at 10·83, 11·04, 11·24, 11·47, 11·96, 12·48, 13·05, 13·23, 13·52, and 13·76 mμ.

2-*Acetylcarbazole* 2 : 4-*dinitrophenylhydrazone*, also obtained as a microcrystalline red solid from acetic acid, had m. p. 303—305° (decomp.) (Found: C, 61·2; H, 4·0%) and different infra-red absorption maxima, *viz.*, 10·01, 10·82, 10·94, 11·10, 11·33, 11·70, 12·04, 12·20, 12·97, 13·36, 13·58, and 13·73 mμ.

3-Benzylcarbazole.—3-Benzoylcarbazole (0·36 g.) in ethanol was hydrogenated over Raney nickel at atmospheric temperature and pressure until absorption (2 mols.) was complete. Evaporation of the filtered solution gave 3-*benzylcarbazole*, colourless plates (from ethanol), m. p. 176° (Found: C, 88·8; H, 5·7; N, 5·3. $C_{19}H_{15}N$ requires C, 88·7; H, 5·8; N, 5·3%).

We thank Dr. S. G. P. Plant for gifts of 2- and 3-acetyl- and 3-benzoyl-carbazole, and the Pressed Steel Company Ltd. for the award of a Fellowship (to R. M. A.).

The Dyson Perrins Laboratory, Oxford. [*Received, February 24th,* 1953.]

390. *The Kinetics of the Iodide-catalysed Reaction between Hydrogen Peroxide and Hydrazine in Acid, Aqueous Solution.*

By P. Davis and W. C. E. Higginson.

In dilute aqueous acid solution the oxidation of hydrazine by hydrogen peroxide is catalysed by iodide ions. Kinetic experiments show that hydrogen peroxide oxidises iodide to iodine which in turn oxidises hydrazine to nitrogen.

It is suggested that traces of transition-metal ion impurities are responsible for the reaction observed in the absence of deliberately added catalysts in neutral and alkaline solutions, and that there is no satisfactory evidence for a direct reaction between hydrogen peroxide and hydrazine under these conditions.

The kinetics of the uncatalysed reaction between hydrogen peroxide and hydrazine, $2H_2O_2 + N_2H_5^+ \longrightarrow 4H_2O + H^+ + N_2$, have been studied in aqueous solution by Gordon (Third Symposium on Combustion, Flame, and Explosion Phenomena, Univ. Wisconsin, 1948, p. 483). Our experiments have however led us to believe that with ordinary " pure " reagents the reaction is catalysed by traces of transition-metal ions, and we know of no convincing evidence for a direct reaction. The results of some of these experiments, referred to in detail by Davis (Thesis, Manchester, 1951), are briefly summarised in the Experimental section of this paper. In developing a method for the estimation of hydrogen peroxide and hydrazine present in the same sample, we found that the iodide ion was under certain conditions a good catalyst for the reaction between these substances, and this paper describes our investigation of this catalysis. In solutions of pH 0 to 1, the catalytic effect of trace-metal impurities when ordinary " pure " reagents are used is much lower than at higher pH values, and these conditions are suitable for a study of the catalytic effect of the iodide ion. Experiments were also done at pH 4, and here small concentrations of ethylenediaminetetra-acetate were used to minimise catalysis by traces of metal ions, a procedure found effective in the study of the direct reaction.

The iodide ion acts as a catalyst in the decomposition of hydrogen peroxide, and its effect has been ascribed to occurrence of the reactions:

$$2H^+ + H_2O_2 + 2I^- \longrightarrow 2H_2O + I_2$$
$$H_2O_2 + I_2 \longrightarrow 2H^+ + O_2 + 2I^-$$

(see, *e.g.*, Baxendale, " Advances in Catalysis," Academic Press Inc., New York, Vol. 4, p. 35). In a similar way the simplest interpretation of the catalytic effect of iodide in the hydrogen peroxide–hydrazine reaction would seem to be in terms of the separate reactions:

$$2H^+ + H_2O_2 + 2I^- \longrightarrow 2H_2O + I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$N_2H_5^+ + 2I_2 \longrightarrow 5H^+ + N_2 + 4I^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Under our conditions the rate of oxidation of hydrogen peroxide by iodine can be neglected in comparison with the rates of these two reactions. If equivalent initial concentrations of hydrogen peroxide and hydrazine are used and these reactions alone are important, a stationary concentration of iodine should be set up and, together with the corresponding reaction velocity constant, can be calculated if the rate laws for reactions (1) and (2) are known. For (1),

$$-\mathrm{d}[H_2O_2]/\mathrm{d}t = \mathrm{d}[I_2]/\mathrm{d}t = k_1[H_2O_2][I^-] + k_2[H_2O_2][I^-][H^+] = k'[H_2O_2],$$

and at the ionic strength (0·575) of our experiments, $k_1 = 0{\cdot}80$ mole^{-1} l. min.$^{-1}$, and $k_2 = 10{\cdot}0$ mole^{-2} l.^{2} min.$^{-1}$ (Bell, Gill, Holden, and Wynne-Jones, *J. Phys. Colloid Chem.*, 1951, **55**, 874). The kinetics of the oxidation of hydrazine by iodine in acid solution have been studied by Berthoud and Porret (*Helv. Chim. Acta*, 1934, **17**, 32), but their results are not

applicable under our conditions. Using 0·002—0·020M-iodide ion, Mr. Marshall in this laboratory has found by similar methods that the rate equation for this reaction is:

$$-\frac{2d[N_2H_5^+]}{dt} = -\frac{d[\text{Iodine}]}{dt} = \frac{k_3[N_2H_5^+][I_2]}{[I^-] + k_4} = k''[N_2H_5^+],$$

Here [Iodine] = $[I_2] + [I_3^-]$, and $[I_2]$ is calculated from [Iodine] and $[I^-]$ by using the dissociation constant of I_3^-. Davis and Gwynne's work (*J. Amer. Chem. Soc.*, **1952**, **74**, 2748) shows that this constant varies little with ionic strength, and accordingly a value of 0·00130 mole l.$^{-1}$ has been used. At 25°, and ionic strength = 0·575, and with $[H^+]$ = 0·479M, k_3 was found to equal 2·33 min.$^{-1}$, and k_4, 0·00071 mol l.$^{-1}$. For 0·16—0·50M-hydrogen ion, k_3 is inversely proportional to the hydrogen-ion concentration, while k_4 is independent of the latter.

When these constants are used, the following procedure gives the first-order constant for the catalysed reaction in terms of the total added iodide concentration, provided that the ratio of the hydrogen peroxide and the hydrazine concentration remains constant. For a given total added iodide concentration a value of the stationary iodide-ion concentration is assumed. The corresponding values of the stationary I_2 and I_3^- concentrations can then be found. From the values of $[I^-]$ and $[I_2]$, the rate constant, k'', for the disappearance of total iodine in the hydrazine–iodine reaction can be calculated. For the same total concentration of added iodide, different stationary concentrations of iodide are then assumed, and a plot of $k''/2$ against the stationary iodide concentration is constructed. The linear plot of the rate constant, k', for the formation of iodine in the hydrogen peroxide–iodide reaction, against the iodide concentration is then superimposed. The point at which the two plots intersect gives the rate constant for formation and disappearance of iodine caused by the hydrogen peroxide–iodide and the hydrazine–iodide reaction respectively. For the overall reaction $2H_2O_2 + N_2H_5^+ \longrightarrow 4H_2O + H^+ + N_2$, if $[H_2O_2]_{\text{initial}} = 2[N_2H_5^+]_{\text{initial}}$ and at iodide–iodine equilibrium,

$$-\frac{d[I_2]}{dt}\,(N_2H_5^+\text{–}I_2 \text{ reaction}) = \frac{d[I_2]}{dt}\,(H_2O_2\text{–}I^- \text{ reaction}) = -\frac{d[H_2O_2]}{dt} = \frac{2d[N_2H_5^+]}{dt} = k'[H_2O_2] = k''[N_2H_5^+]$$

Hence is found the first-order rate constant $k = k' = \frac{1}{2}k''$ for the disappearance of hydrogen peroxide and hydrazine at the total added iodide concentration used in the calculation. The corresponding stationary concentration of iodine ($[I_2] + [I_3^-]$) is also known since $[I_2]$ and $[I_3^-]$ are evaluated in calculating the rate constant.

TABLE 1. $[H_2O_2]_{\text{initial}} = 0{\cdot}05M$; $[N_2H_4,H_2SO_4]_{\text{initial}} = 0{\cdot}025M$; $[H^+] = 0{\cdot}479M$.

Expt.	Added $[I^-]$ $\times 10^3$M	$10^3k_{(\text{obs.})}$ (min.$^{-1}$)	$10^3k_{(\text{calc.})}$ (min.$^{-1}$)	$[\text{Iodine}]_{(\text{obs.})}$ $\times 10^3$N	$[\text{Iodine}]_{(\text{calc.})}$ $\times 10^3$N
1	0·0667	0·443	0·372	<0·05	<0·01
2	0·167	1·10	0·930	<0·05	<0·01
3	0·333	2·15	1·80	<0·05	<0·01
4	0·667	4·26	3·65	<0·05	<0·01
5	1·67	9·04	8·76	<0·05	0·01
6	3·33	12·1	16·0	<0·10	0·03
7	5·00	16·0	22·2	<0·15	0·07
8	6·67	17·7	27·4	<0·20	0·13
9	8·33	21·2	31·7	<0·35	0·19
10	10·0	25·4	35·5	<0·45	0·26
11	13·3	31·6	42·1	<0·60	0·41
12	16·7	35·9	47·5	<0·75	0·56
13	25·0	45·2	58·2	<1·30	1·00
14	33·3	53·0	66·5	<1·60	1·47

In Table 1 calculated and observed values of k, defined above, and of the stationary iodine concentration are tabulated with the corresponding concentration of added iodide for experiments at 0·479M-hydrogen ion. In Table 2 are tabulated similar data at 0·312, 0·160, and 10^{-4} M-hydrogen ion. For these experiments the stationary iodine concentrations were too small to be measured with reasonable accuracy and hence the calculated values are not recorded. At 10^{-4} M-hydrogen ion the solutions remained colourless, showing a very low stationary iodine concentration. Agreement between calculated and

experimental values is fairly good, and we conclude therefore that iodide acts as a redox catalyst in that it is oxidised by the hydrogen peroxide to iodine which in its turn oxidises the hydrazine. It is not possible to be more specific since the detailed mechanisms of the contributing reactions, (1) and (2), are unknown.

TABLE 2. $[H_2O_2]_{initial} = 0{\cdot}05$M; $[N_2H_4,H_2SO_4]_{initial} = 0{\cdot}025$M.

$[H^+]$ M	Added $[I^-]$ $\times 10^3$M	$10^3k_{(obs.)}$ (min.$^{-1}$)	$10^3k_{(calc.)}$ (min.$^{-1}$)	$[H^+]$ M	Added $[I^-]$ $\times 10^3$M	$10^3k_{(obs.)}$ (min.$^{-1}$)	$10^3k_{(calc.)}$ (min.$^{-1}$)
0·312	0·25	1·19	0·98	0·160	6·67	15·0	14·4
0·312	0·50	2·32	1·95	10^{-4}	0·33	0·247	0·254
0·312	2·50	9·88	9·30	10^{-4}	1·67	1·25	1·33
0·312	5·00	14·8	17·3	10^{-4}	3·33	2·42	2·66
0·160	0·33	0·99	0·80	10^{-4}	6·67	4·94	5·32
0·160	1·00	2·89	2·39	10^{-4}	13·3	9·92	10·6
0·160	1·67	4·77	3·98				

The discrepancies between calculated and experimental values may arise partly because the rate constants used were determined under different concentration conditions from those obtaining in the catalysis experiments. Also, for the hydrazine–iodine reaction the predominating anion was chloride, as distinct from perchlorate in the hydrogen peroxide–iodide and the catalysis experiments. In the experiments at low iodide concentrations in 0·160, 0·312, and 0·479M-hydrogen ion, the observed rate constants are somewhat larger than those for the hydrogen peroxide–iodide reaction at the same acidities. At low iodide concentrations the rate constants for the catalysis experiments should closely approach, but should not exceed, those for the hydrogen peroxide–iodide reaction. However, the reaction rates are small and it is possible that this anomaly may be caused by the presence of catalytically active impurities.

In strongly acid solutions iodide is an effective catalyst only at low concentrations, and, with regard to the evolution of nitrogen, the reaction virtually ceases at added iodide concentrations about three times the hydrogen peroxide concentration. Under these conditions the hydrogen peroxide is quantitatively reduced while the iodine so formed reacts very slowly with hydrazine. The analytical method used for determining hydrogen peroxide in the presence of hydrazine depends in part upon these circumstances.

EXPERIMENTAL

Materials.—Hydrogen peroxide stock solutions were prepared by dilution of the Laporte, stabiliser-free product; sodium iodide was of B.P. recryst. quality; sodium perchlorate was Hopkin and Williams' recrystallised product. Ethylenediaminetetra-acetic acid (disodium salt) was obtained from Siegfried, Zofingen; other reagents were of B.D.H. "AnalaR" quality. Demineralised water, of conductivity not greater than $1{\cdot}5 \times 10^{-7}$ mhos when prepared, was obtained by passing distilled water through a column of "Bio-deminrolit F" mixed exchange resin (Permutit Co.).

Analysis.—All stock oxidising and reducing solutions used, including the sodium iodide solutions, were ultimately referred to potassium iodate as primary standard Hydrogen peroxide was estimated in the reaction mixture by adding a sample to sufficient 3M-sulphuric acid to make the solution approx. molar in hydrogen ion. Solid potassium iodide was immediately added to give 0·5—1·0M-iodide ion, and the iodine liberated was titrated with 0·1N-sodium thiosulphate, the solution being agitated throughout the titration. 0·1N-Iodine, in small excess over the amount equivalent to the hydrazine present, was then added and the mixture buffered to approximately pH 5 by addition of the appropriate amount of concentrated sodium acetate solution. After 2 min., the excess of iodine was back-titrated against 0·1N-sodium thiosulphate. By this procedure hydrogen peroxide and hydrazine concentrations could be determined with an accuracy of $\pm 0{\cdot}0004$M and $\pm 0{\cdot}0002$M respectively, as shown by experiments with catalyst-free solutions under similar conditions. To obtain the true hydrogen peroxide concentration in the experiments at high iodide concentration in 0·479M-acid it was necessary to subtract the concentration of iodine already present in the reaction mixture from the hydrogen peroxide concentration found by the above method. When the reactants were mixed at the beginning of a kinetic experiment the iodine concentration increased for *ca.* 3 min. and then, within a random error of about $\pm 10\%$, was constant for the remainder of the reaction. The comparative slowness with which the stationary concentration

was established enabled a fairly close upper limit to be obtained by rapid titration of a sample of reaction mixture with 0·1N-sodium thiosulphate. Since the stationary iodine concentrations were much smaller than the initial hydrogen peroxide concentration, the errors introduced in correcting to the true hydrogen peroxide concentration were unimportant except towards the end of the reaction. Concentrations of reactants were not determined after reaction was about 85% complete.

Kinetic Experiments.—Experiments were done at 25° under nitrogen in a vessel fitted with a mercury-sealed stirrer. Samples for analysis were withdrawn by pipette. All stock solutions used in making up the reaction mixture were prepared with demineralised water. Initial concentrations of hydrogen peroxide and hydrazine were 0·05M and 0·025M respectively, except for experiments 9 to 14 (Table 1) where extra hydrogen peroxide, approximately equivalent to the stationary iodine concentration, was used. Hydrazine was added as monohydrazine sulphate, $N_2H_4.H_2SO_4$. In calculations of the hydrogen-ion concentration, 0·08 mole $l.^{-1}$ was used for the second dissociation constant of sulphuric acid at an ionic strength of 0·575. This value was obtained by a short extrapolation from Bray and Liebhafsky's results (*J. Amer. Chem. Soc.*, 1935, **57**, 51). In the reaction solution, sodium iodide was preferred to potassium iodide since potassium perchlorate precipitates were obtained with the latter. In the experiments at pH 4 an acetic acid–sodium acetate buffer was used and the reaction solutions contained 0·002M-ethylenediaminetetra-acetate to minimise catalysis by traces of metal ions (see below). For all the kinetic experiments the stoicheiometry was within the limits $\Delta[H_2O_2]/\Delta[N_2H_5^+] = 2{\cdot}00 \pm 0{\cdot}04$. For most of the kinetic experiments eight determinations of reactant concentrations were made at suitable time intervals.

The Direct Reaction between Hydrogen Peroxide and Hydrazine in Aqueous Solution.—Before studying the iodide-catalysed reaction we had investigated the possibility of a direct reaction between hydrogen peroxide and hydrazine. The method of analysis described above was used. In experiments at pH 9·5 and 13 we found that the rate of disappearance of both reactants was of the first order with respect to hydrogen peroxide if the hydrazine was in similar concentration to the hydrogen peroxide ($\simeq$ 0·05M), or was in 20—40-fold excess. With hydrogen peroxide in 20-fold excess (0·80M) the rate was constant for the first 50% reaction but then slowly diminished. Repurification of the reagents and the use of demineralised water gave lower rates of reaction, but consistent results could not be obtained except when experiments were repeated with the same stock solutions. The order of reaction was again as described above. These observations suggest that the rate-determining step involves reaction between hydrogen peroxide and an impurity. At pH 9·5 the addition of small amounts of copper(II) caused a very large increase in the rate of reaction; at this pH, 10^{-7}M-copper(II) would be sufficient to account for the rates observed with "pure" reagents. Other transition-metal ions were effective, but much less so than copper(II).

In the presence of small amounts of ethylenediaminetetra-acetate, generally 2% of the initial concentrations of the reactants, and in one case 0·05%, the rate of reaction was very much lower than that obtained with purified reagents under otherwise similar conditions (see Table 3). We conclude that traces of transition-metal ions were not removed in our purification

TABLE 3.

pH	9·05	9·5	9·5	9·5	10·3	10·7	11·6	13	13
10^3k (min.$^{-1}$) (Gordon)	2·75	—	—	—	4·76	9·27	2·75	—	—
10^3k (min.$^{-1}$) (this work)	—	6·7	0·09	0·08	—	—	—	1·17	0·138
10^3[enta] (M)	—	—	0·05	2·0	—	—	—	—	2·0

procedures, and that the ethylenediaminetetra-acetate ion greatly reduced the concentration of these catalytically active species in forming the corresponding inactive or much less active complex ions. We regard this as a more likely explanation than that the effect of the complex-forming reagent is to decrease the length of reaction chains by reaction with radical intermediates.

In Table 3 are tabulated typical rate constants found in the presence and absence of ethylenediaminetetra-acetate (enta), together with first-order rate constants, also at 25°, calculated from Gordon's work (*loc. cit.*). Our first-order rate constants are defined as $-k = d(\ln[H_2O_2])/dt = d(\ln[N_2H_5^+])/dt$, as for the iodide-catalysed reaction; concentrations were $H_2O_2 = 0{\cdot}100$M, $N_2H_5^+ = 0{\cdot}050$M. The rate constants from Gordon's work are equivalent, and are found from the expression $d[N_2]/dt = k[N_2H_5^+]$, though no indication of the order of the reaction is given. In his experiments, in which the initial reactant concentrations were both 1·5M, presumably only the initial rates of nitrogen formation were measured. It can be

seen that at similar hydrogen-ion concentrations our rate constants in the absence of ethylenediaminetetra-acetate are similar to Gordon's, but that in the presence of this reagent we obtained substantially lower values. Since in our experiments the residual reaction in the presence of the complexing reagent still showed first-order kinetics, we consider that a direct reaction between hydrogen peroxide and hydrazine in dilute aqueous solution can account for a small proportion only of the total reaction rate normally observed unless special measures are taken to remove catalytically active impurities. Thus we think it possible that Gordon was studying the reaction catalysed by traces of metal ions, though the relatively high concentrations of reactants he used are admittedly more favourable to the occurrence of the direct (second-order) reaction than are our conditions. We conclude therefore that his results do not provide unequivocal evidence for an uncatalysed reaction between hydrogen peroxide and hydrazine in aqueous solution.

THE UNIVERSITY, MANCHESTER, 13. [*Received, March 14th*, 1953.]

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391. *Reactions of Unsaturated Compounds. Part X.* The Oxidation of Camphene by Chromic Oxide.*

By W. J. HICKINBOTTOM and D. G. M. WOOD.

(±)-Camphene is oxidised by chromic oxide in acetic anhydride, to give camphene oxide as the first product. Camphene oxide is reduced by lithium aluminium hydride in ether to 2-methylcamphenilol.

TREIBS and SCHMIDT (*Ber.*, 1928, **61**, 464) reported that oxidation of camphene by chromium trioxide in acetic anhydride gave camphenilone, camphenilanic acid, and probably camphenilanaldehyde. Our experience of this type of oxidation with 2 : 4 : 4-trimethylpent-1- and -2-ene and with di*neo*pentylethylene (*J.*, 1948, 1334; 1951, 1600) suggests that neither the acid nor the aldehyde is a primary product of the oxidation, but that they result from the initial formation of an epoxide which isomerises under the conditions used by Treibs and Schmidt to an aldehyde and thence by oxidation to the acid.

Oxidation of camphene by chromic oxide in acetic anhydride, with such modification of Treibs and Schmidt's technique as was considered necessary to prevent isomerisation of the epoxide, gave camphene oxide and a high-boiling complex mixture.

The satisfactory identification of camphene oxide by comparison of melting points is difficult owing to the existence of stereoisomeric forms. The recorded melting points for (±)-camphene oxide are 86—88° (Arbusov, *J. Gen. Chem. Russia*, 1939, 255) and 96—104° with semi-solid and liquid products (Hückel and Kirschner, *Chem. Ber.*, 1947, **80**, 46). Crude (±)-camphene oxide, prepared from (±)-camphene by oxidation with perbenzoic acid, gave on sublimation at 25 mm., two batches, (*a*) m. p. 84—86° and (*b*) m. p. 78—92°, resolved by chromatography into fractions, m. p. 84—86° and 96—98°, but no further separation could be obtained. It is unlikely that these differences in melting point can be due to partial isomerisation to camphenilanaldehyde, m. p. 76°, during the separation, since no detectable amount of camphenilanol could be obtained from the reduction of the epoxide (see below).

Each of the fractions isomerised to camphenilanaldehyde under the influence of acids. Attempts to hydrate the epoxides by boiling aqueous alcohol for 24 or 60 hr. gave no glycol but only camphenilanaldehyde. The camphene oxide was identified by reduction in ether with lithium aluminium hydride. A mixture of tertiary alcohols was obtained from which only 2-methylcamphenilol could be characterised (as *p*-nitrobenzoate). The presence of camphene hydrate was inferred from the melting point of some of the fractions resulting from chromatography of the crude alcohol, but attempts to isolate it were unsuccessful. The preparation of crystalline esters of camphene hydrate is difficult and gives poor yields (cf. Hückel, *Annalen*, 1941, **549**, 201). In the reduction product, no camphenilanol could be detected, although this alcohol forms a *p*-nitrobenzoate readily and with ease. The

* Part IX, *J.*, 1951, 1600.

absence of noticeable amounts of this alcohol excludes the presence of an appreciable amount of camphenilanaldehyde in the camphene oxide.

A search was made for camphenilone among the oxidation products. It was first established that the 2 : 4-dinitrophenylhydrazones of camphenilone and camphenilanaldehyde could be separated by chromatography on alumina. These fractions of the oxidation product which might be expected to contain camphenilone were converted into 2 : 4-dinitrophenylhydrazones in acid aqueous alcohol, any epoxide present being thus isomerised to camphenilanaldehyde. Camphenilone could not be detected.

Experimental

Preparation of (±)-Camphene Oxide.—Reaction of (±)-camphene (15·6 g.) in chloroform (20 ml.) with a solution of perbenzoic acid (23·1 g.) in chloroform (430 ml.) at 0° was substantially complete in 45 min. The crude epoxide, b. p. 87—96/25 mm., was separated by sublimation at 25 mm. into fractions, (a) m. p. 84—86° (3·6 g.) and (b) m. p. 78—92° (5·4 g.), which on chromatography on alumina from 1 : 1 benzene–light petroleum (b. p. 40—60°), with elution by ether, gave fractions, m. p. 94—98°, 96—98°, 92—100°, 94—96°, and 84—86°, respectively. Each fraction, with a warm aqueous acid solution of 2 : 4-dinitrophenylhydrazine, gave the 2 : 4-*dinitrophenylhydrazone*, yellow needles (from alcohol), m. p. 151°, of camphenilanaldehyde (Found : C, 57·7; H, 6·5; N, 16·9. $C_{16}H_{20}O_4N_4$ requires C, 57·8; H, 6·1; N, 16·9%).

Aqueous mineral acid isomerised the epoxide to aldehyde, with no evidence of hydration.

Reduction of Camphene Oxide.—A solution of the oxide (8·0 g.) in dry ether (50 ml.) was added dropwise to an ethereal solution of lithium aluminium hydride (1·1 g.) at such a rate that the stirred solution gently refluxed. The reduction was completed by 30 min.' further boiling. The solution was then poured on ice and sufficient dilute sulphuric acid to give two homogeneous layers. The ethereal layer was added to ethereal extracts of the aqueous solution. Evaporation of the washed ethereal solution gave a semi-solid product (8·0 g.) with a smell unlike that of the oxide. It did not react with an acid solution of 2 : 4-dinitrophenylhydrazine, showing the absence of unchanged epoxide. The alcoholic product (Found : C, 77·5; H, 12·0. Calc. for $C_{10}H_{18}O$: C, 77·9; H, 11·8%) consisted mainly of 2-methylcamphenilol. The absence of any appreciable amount of camphenilanol was shown by converting the crude alcohol into the *p*-nitrobenzoate and chromatographing this on alumina [light petroleum (b. p. 40—60°)–benzene]. The *p*-nitrobenzoate, m. p. and mixed m. p. 143°, of 2-methylcamphenilol was the only product. The presence of camphene hydrate in the product of reduction was suggested by chromatographing the crude mixture (Al_2O_3; light petroleum), which gave fractions with m. p. from 95—120° to 125—139°. But no more effective separation of the higher-melting solid could be obtained, nor could a crystalline derivative of camphene hydrate be prepared from it.

Oxidation of Camphene by Chromium Trioxide in Acetic anhydride.—(a) *Isolation of camphene oxide.* The following is typical of a number of oxidations, in which 25—75 g. of camphene were used. Chromium trioxide (19 g.) in acetic anhydride (170 ml.) was added slowly to a stirred solution of camphene (50 g.) in carbon tetrachloride (200 ml.) cooled in ice–salt. After 2 hr. the product was hydrolysed, while still in an ice-bath, by ice and aqueous sodium hydroxide (80 g. in 400 ml.). Any precipitate was removed by the addition of just sufficient acetic acid. The aqueous layer was extracted rapidly with ether. The combined carbon tetrachloride layer and ethereal extracts were thoroughly shaken with aqueous alkali before being dried. Distillation gave camphene (29 g.), crude camphene oxide (4·1 g.), b. p. 60—86/22 mm., and a high-boiling residue (A) (3·5 g.).

The crude oxide was freed from a small amount of admixed camphene by chromatography on alumina to give a specimen, m. p. 76—84° (Found : C, 79·0, 79·1; H, 10·5, 10·4. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%). Its identity was established by comparison with authentic camphene oxide, by isomerisation by dilute sulphuric acid to camphenilanaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 151°), and by reduction by lithium aluminium hydride to 2-methylcamphenilol (*p*-nitrobenzoate, m. p. and mixed m. p. 143—144°).

(b) *Attempted isolation of camphenilone.* The fractions intermediate in b. p. between camphene and camphene oxide might have contained camphenilone. They were treated with 2 : 4-dinitrophenylhydrazine in aqueous-alcoholic sulphuric acid and the resulting dinitrophenylhydrazones chromatographed as described below. Only the derivative of camphenilanaldehyde was obtained.

An artificial mixture of the 2 : 4-dinitrophenylhydrazones (100 mg. each) of camphenilone

and of camphenilanaldehyde was absorbed on alumina from a 2 : 1 (v/v) light petroleum (b. p. 40—60°)–benzene. Development with 19 : 1 (v/v) light petroleum (b. p. 40—60°)–ether gave two bands; the lower gave camphenilone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 161°; the upper gave the derivative, m. p. and mixed m. p. 151°, of camphenilanaldehyde.

No separation was observed on a silica column (cf. Roberts and Green, *Ind. Eng. Chem. Anal.*, 1946, **18**, 335).

Camphenilone was prepared from camphene by the method described by Snitter (*Bull. Soc. Pin.*, 1933, [2], 178. *Brit. Abs.*, 1933, 1300) and Blaise (*Bull. Soc. chim.*, 1900, **23**, 164). It gave a 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethyl alcohol), m. p. 161° (Found : C, 56·6; H, 5·7; N, 17·4. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%).

(c) *The high-boiling residues.* The combined residues (A) from all the camphene oxidations were distilled at 1 mm., giving viscous unsaturated liquids boiling between 60° and 150°, which could not be separated. The fractions boiling up to 100°/1 mm. gave smaller or greater amounts of a 2 : 4-*dinitrophenylhydrazone*, needles (from aqueous acetic acid), m. p. 222—223°, almost insoluble in ether or ethyl alcohol (Found : C, 55·9; H, 5·4; N, 15·8. $C_{16}H_{18}O_5N_4$ requires C, 55·5; H, 5·2; N, 16·2. $C_{16}H_{16}O_5N_4$ requires C, 55·8; H, 4·7; N, 16·3%).

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392. *Heats of Combustion and Formation of Some Linear Polydimethylsiloxanes; the* Si–C *and* Si–O *Bond-energy Terms.*

By RAYMOND THOMPSON.

The heats of combustion of the four lowest linear polydimethylsiloxanes (DC200 fluids) have been measured in a commercial bomb calorimeter of single-valve type. Combustion of these compounds is not complete under the conditions usually employed for an organic liquid, and an insulating skin of silica formed on the surface of the burning liquid prevents complete combustion of that beneath. A technique in which a glass ampoule containing the liquid bursts explosively at the time of firing is described. Under such conditions the liquids were found to burn quantitatively to silica, carbon dioxide, and water according to the equation :

$$CH_3{\cdot}[SiMe_2{\cdot}O]_n{\cdot}SiMe_3\ (l) + (4n + 8)O_2\ (g) = (n + 1)SiO_2\ (s) + (2n + 4)CO_2\ (g) + (3n + 6)H_2O\ (l)$$

The following heats of combustion (at 22°) were obtained [in kcal./mole (abs. k-joules/mole in parentheses)] : hexamethyldisiloxane, 1401 (5863); octamethyltrisiloxane, 1860 (7784); decamethyltetrasiloxane, 2289 (9578); dodecamethylpentasiloxane, 2756 (11,530). Energy increments are approximately equal for each $\cdot SiMe_2{\cdot}O\cdot$ unit added, and values for the heats of formation of the compounds are calculated to be 194 kcal./mole (812 abs. k-joules/mole), 337 (1410), 509 (2130), and 643 (2690) respectively. The heats of formation from monatomic gases have been calculated and, by application of simultaneous equations to the results obtained, the Si–C and Si–O bond-energy terms are deduced. The strength of the C–H linkage being assumed to be the same as in the paraffins, the Si–C energy term is found to be 64 kcal./mole (on the basis of 171·7 kcal./g.-atom for the heat of atomisation of carbon); a value of 117 kcal./mole has been obtained for the Si–O linkage. The observed heats of formation of other organo-silicon compounds are compared with values calculated by using bond-energy terms derived as above and with those obtained from the heats of formation of carborundum and silica.

ATTENTION has recently been drawn (*J.*, 1952, 3292) to the difficulties encountered in obtaining from combustion data the heats of formation of organic compounds containing

elements other than carbon, hydrogen, nitrogen, and oxygen. There is, in consequence, little published information concerning such heats of formation, and in particular about the thermochemically derived strength of the linkage between carbon and the " other " element. Major difficulties of combustion calorimetry often relate to the ascertainment of an equation for the bomb reaction, and it is somewhat surprising to find that little attention has been paid to the thermochemistry of organo-silicon compounds, in which the reaction is unusually straightforward provided that complete combustion is attained. Data concerning the heats of combustion of five organo-silicon compounds have recently been reported by Tanaka, Takahishi, Okawara, and Watase (*J. Chem. Phys.*, **1951**, **19**, 1330), and the heat of formation of ethyl orthosilicate has been estimated from its heat of hydrolysis by Ogier (*Ann. Chim. Phys.*, 1880, **20**, 5). However, comparison of the observed ΔHf° values and those calculated from published values for the energy terms of the bonds concerned (*e.g.*, Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1945) reveals that revision of these energy terms is necessary (see Table 5). There has previously been no systematic investigation designed to provide fundamental quantitative data, and the present experiments were undertaken with the aim of beginning to fill this gap.

The polydimethylsiloxane homologous series is $CH_3{\cdot}[SiMe_2{\cdot}O]_n{\cdot}SiMe_3$, with values of n from unity up to 2000 or more. The compounds burned in the course of this research were the first four members. In conformity with other work on these compounds the symbols employed by Wilcock (*J. Amer. Chem. Soc.*, 1946, **68**, 691) are used here: M denotes the end-group $SiMe_3{\cdot}O_{\frac{1}{2}}$ and D represents the incremental group $[SiMe_2{\cdot}O]$.

Experimental

Materials.—The polydimethylsiloxanes used were DC200 liquids supplied by Midland Silicones Ltd. This series is classified according to viscosity, the liquids of 0·65, 1·0, 1·5, and 2·0 centistokes corresponding fairly closely with M_2, M_2D, M_2D_2 and M_2D_3, respectively. That the materials were substantially pure before distillation was indicated by the narrow boiling range of each (<2°). The liquids were further twice distilled before use, the middle fraction of the first distillation being again distilled and the middle fraction of the second distillation taken for combustion. The b. p.s of the purified samples are listed, together with the temperatures quoted by Wilcock (*loc. cit.*) and Patnode and Wilcock (*J. Amer. Chem. Soc.*, 1946, **68**, 358) in Table 1.

Table 1.

Compound	Wilcock	Patnode and Wilcock	Present work
M_2	100°/757 mm.	100°/760 mm.	100°/759 mm.
M_2D	151·7°/747 mm.	153°/760 mm.	153°/774 mm.
M_2D_2	194°/760 mm.	194°/760 mm.	194°/760 mm.
M_2D_3	229°/760 mm.	229°/760 mm.	228·5°/766 mm.

The complete identity of the infra-red absorption spectrograms (wave-length 2—15μ) obtained from the present samples with those in the literature (Wright and Hunter, *ibid.*, 1947, **69**, 803) was further evidence of purity. A Perkin–Elmer Model 21 double-beam recording spectrophotometer was used in the present work.

Calorimetry.—The apparatus was the standard commercial Mahler–Coòk bomb calorimeter, incorporating a 300-ml. stainless-steel bomb of the single-valve type and a Beckmann thermometer. The liquids, being volatile, were sealed into thin glass ampoules before weighing and combustion. It was found, however, that the normal techniques of combustion of a liquid could not be applied to organo-silicon compounds, for despite the observation by Tanaka *et al.* in connection with their compounds, the liquids were not found to " burn smoothly." If a single ampoule, designed to collapse during the process of charging the bomb with oxygen, was employed, combustion was incomplete; the silica produced during the early stages of combustion formed an insulating layer on the surface of the liquid so that access of oxygen was denied to that beneath and much carbon and incompletely burnt silicone were left on the base of the crucible. This also happened if the ampoule merely collapsed at the time of ignition. (It is rather surprising that Tanaka *et al.*, while giving full details of ampoule dimensions, did not indicate that other than the normal technique for the combusion of a liquid is necessary for organo-silicon compounds. Although the compounds employed in the present research did

not include those which they burned, their materials contained similar percentages of silicon and it seems most likely that the silica produced would interfere with combustion. Since these authors claim an overall uncertainty in their values of not more than ±0·10%, weights of materials burned were presumably assessed by determination of the water and carbon dioxide produced.)

For the combustion of the liquids in quantities conducive to accuracy in weighing and measuring temperature rise, it was found that the ampoule should burst explosively at the moment of electrically firing the charge, and scatter the siloxane throughout the (dry) bomb. When this happened, combustion was complete. But the preparation of an ampoule strong enough not to collapse at 25 atm. and yet to be capable of being burst by the heat generated by the fuse (of, say, 25 cal.) was largely a matter of chance: a stronger ampoule will burst readily if a large fuse, or promoter such as benzoic acid, is used; use of a large amount of promoter is undesirable since it is then responsible for much of the observed temperature rise. However, as the (lower) polydimethylsiloxanes are themselves readily ignited, it was decided to employ the liquid as its own promoter. This was effected by dividing the sample approximately equally between two ampoules, one of which was designed to collapse at a pressure of several atmospheres to produce a pool of liquid in the crucible; the other was designed to burst a fraction of a second after firing owing to the heat produced by the combustion of the liquid from the first. The ampoules were spheres of soft glass approximately 1 cm. in diameter and having a 1-cm. tail of 1 mm. bore, sealed at the tip. The weaker ampoules weighed between 0·07 and 0·10 g., and the stronger 0·4—0·7 g. The latter were temporarily sealed at the tip and pre-tested to 25 atm. before being filled. All were filled from a hypodermic syringe having a gauge 14 needle, and the combined weight of sample of about 0·8—1·0 g. gave a temperature rise in the range 1·5—2°. Ignition was effected by applying 12 v to a 4 × 0·009 cm. platinum wire, with 0·005—0·007 g. of dried Whatman No. 1 filter-paper (3·99 kcal./g.) as a fuse. It should be emphasised that for complete combustion it is essential that the crucible as well as the ampoules be shattered. Since one crucible per combustion was thus required, a less expensive alternative to the usual silica was sought. (A shallow crucible of stainless steel 3 cm. in diameter had been tried, but although the maximum depth was only about 2 mm. the pool of liquid did not burn completely.) The most satisfactory substitute was found to be the bottom of a thin-walled 1″-diameter glass boiling-tube, cut to a depth of ¾″ and with lips pulled out as on the orthodox (Mahler–Cook) combustion bomb crucible.

Under the above conditions combustion was complete and results were reproducible almost to the maximum precision attainable with the apparatus. Five determinations were made with each liquid, the results of which are recorded in Table 2.

TABLE 2.

Compound	M.W.	Heat of combustion, kcal./mole	Mean
M_2	162·32	1396, 1412, 1406, 1397, 1394	1401
M_2D	236·45	1858, 1864, 1867, 1851, 1858	1860
M_2D_2	310·58	2297, 2285, 2291, 2280, 2290	2289
M_2D_3	384·71	2767, 2754, 2738, 2764, 2756	2756

The relative mean deviation of the water equivalent value of the apparatus was about 0·2%, a deviation high by comparison with modern precision techniques but of sufficient precision for bond-energy term purposes in view of the other uncertainties involved. Allowance has been made for nitric acid formation, and results are corrected to 15°-calories, but no other Washburn corrections were applied and weights were not corrected to vacuum. The determinations were made at a temperature of 22° ± 1°; for subsequent calculations the heats of formation at 25° are considered to be the same. No correction has been applied for heat of adsorption on to silica of the water and nitric acid formed during combustion.

Stoicheiometry and Analysis.—The inside surfaces of the bomb were, after combustion, covered with a loosely-adherent layer of finely divided silica, the fragments of broken glass lying at the bottom. The silica was found by *X*-ray powder photography to be completely amorphous. Pieces of glass which had been melted were often dark, but Jessup (*J. Res. Nat. Bur. Stand.*, 1937, **18**, 115, RP 966) has shown that such darkening is not of thermochemical significance. The contents of the bomb were washed quantitatively into a tared asbestos Gooch crucible and dried for 3 hr. at 140°. The use of a trimmed feather instead of a rubber "policeman" was found to be of considerable advantage in the operation of transferring the silica. Silicon contents of the various liquids were found to be as follows: M_2, calc. 34·50, found 34·2,

34·1; M_2D, calc. 35·5, found 35·0; M_2D_2, calc. 36·10, found 36·1; M_2D_3, calc. 36·50, found 36·3%.

The results are seen to be generally lower than the calculated values. This is considered not to be a reflection upon the purity of materials, of which b. p. and range and infra-red absorption spectra provide better indications, or upon the combustion. Complete transference of the dispersed silica from the complex inner surfaces of the bomb is difficult; there is also the possibility of slight loss by solution of the fine silica in the wash water.

Results and Discussion

The equation given on p. 1908 being used, together with $\Delta Hf°$ values of −94·05 and −68·32 kcal./mole (Wagman, Kilpatrick, Taylor, Pitzer, and Rossini, *J. Res. Nat. Bur. Stand.*, 1945, **34**, 143) for the heats of formation of carbon dioxide and water, respectively, and a $\Delta Hf°$ value of −208·14 kcal./mole for amorphous silica (calculated from the results of Humphrey and King, *J. Amer. Chem. Soc.*, 1952, **74**, 2041), heats of formation ($\Delta Hf°$) of the siloxanes are calculated to be: M_2, −194; M_2D, −337; M_2D_2, −509; M_2D_3, −643 kcal./mole. When these values are plotted against molecular weight the four points fall close to (alternately on either side of), but not exactly on, a straight line. If it is assumed that the energy increments between successive members of the series will be equal, the values obtained for $\Delta Hf°$ by interpolation from this straight line are −189, −343, −496, and −649 kcal./mole. It is not possible, however, to distinguish between the deviation from linearity attributable to experimental error and that arising from other factors. It is to be noted that the oscillation of physical properties (including the wave-length shift of ultra-violet absorption peaks) is more pronounced than is usual in homologous series, and the heats of formation may in some way be affected also.

With a knowledge of the heats of formation of the polydimethylsiloxanes in their standard states, it is now possible to assign values for the heats of formation of the gaseous compounds from atoms of the elements. The latent heats of evaporation of the liquids are known from the work of Wilcock (*loc. cit.*) and are reproduced in Table 3; heats of atomisation of the constituent elements (other than carbon) are known with an accuracy probably commensurate with that of the heats of combustion. The heats of formation in the gaseous state from atoms, $-\Delta E$, have therefore been calculated from the heats of combustion of these compounds of formula $C_aH_bO_cSi_d$ by use of the expression:

$$-\Delta E = Q_{comb.} + L_{vap.} - 265{\cdot}7a - 86{\cdot}25b - 59{\cdot}16c - 296{\cdot}2d$$

The values for the heats of atomisation involved in the *a*, *b*, *c*, and *d* terms are taken from "Selected Values of Chemical Thermodynamic Properties" (Nat. Bur. Stand., Washington, 1950). Values of 52·098 and 59·159 kcal./g.-atom are now generally accepted for hydrogen and oxygen, respectively. The corresponding value for carbon may still be regarded as a matter of some controversy, later evidence tending strongly towards a value of the order of 170 rather than 125 kcal./g.-atom (Marshall and Norton, *J. Amer. Chem. Soc.*, 1950, **72**, 2166, and references cited therein) although evidence for a value of about 141 has recently been strengthened (Doehard, Goldfinger, and Waelbroeck, *J. Chem. Phys.*, 1952, **20**, 757); the actual figure of 171·7 kcal. incorporated in the *a* term above is taken from Brewer, Gilles, and Jenkins (*ibid.*, 1948, **16**, 797) and is that quoted in "Selected Values," etc. The heat of atomisation of silicon is reported to be 88·04 kcal./g.-atom (*op. cit.*; unpublished work of Brewer *et al.*). $-\Delta E$ values of the four polydimethylsiloxanes are listed in Table 3.

Table 3.

Compound	$L_{vap.}$ (kcal./mole)	$-\Delta E$ (kcal./mole)	Incremental change in $-\Delta E$
M_2	8·3	2389	
			944
M_2D	9·45	3333	
			973
M_2D_2	11·5	4306	
			936
M_2D_3	12·7	5242	

Si–C *and* Si–O *Bond-energy Terms.*—Three types of bond are involved in the breakdown of these compounds, namely, C–H, Si–C, and Si–O. Since the *ratio* of the Si–C to Si–O

linkages varies as the series is traversed, it is possible, after certain assumptions, to evaluate the strength of a particular type of bond by application of simultaneous equations to $-\Delta E$ values of any two of the homologues. The only bonds involved are single, largely covalent linkages and no contribution is made by resonance or strain energy in the normally accepted sense of these terms. The equations employed are :

$$E_{M_3} = 6E_{Si-C} + 2E_{Si-O} + 18E_{C-H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$E_{M_2D} = 8E_{Si-C} + 4E_{Si-O} + 24E_{C-H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$E_{M_2D_2} = 10E_{Si-C} + 6E_{Si-O} + 30E_{C-H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$E_{M_2D_3} = 12E_{Si-C} + 8E_{Si-O} + 36E_{C-H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

These four equations can be solved in six different ways; solutions are listed in Table 4, from the mean values of which the Si–C and Si–O energy terms are found to be 64 and 117 kcal./mole, respectively.

In practical application to the siloxane type of compound the Si–C and Si–O energy terms are frequently taken together; it will be seen from cols. *C* and *D* that the summation reduces the range of deviation. The energy term for the Si–C linkage is based on the assumption that the strength of the C–H bonds of the methyl group when the carbon is directly attached to the silicon is the same as when it is attached to another carbon atom, since the equations can be solved only for (Si–C + 3C–H). A difference of 1 kcal./mole

TABLE 4.

Pairs of equations	*A.* Si–C	*B.* Si–O	*C.* Si–C + Si–O	*D.* 3Si–C + Si–O
(1) and (2)	65	111	176	306
(1) and (3)	62	122	184	308
(1) and (4)	64	116	180	308
(2) and (3)	53	139	192	298
(2) and (4)	60	121	181	301
(3) and (4)	78	94	172	328
Mean	64	117	181	308
Calc. from $\Delta Hf°$ SiC and SiO_2	72	104	176	320

in the mean strength of the C–H bond (*e.g.*, by taking the mean C–H value of methane rather than of the C–H bonds of the CH_2 group, see below) would, of course, alter the Si–C value by 3 kcal./mole; however, in many polysiloxanes the two types of bond are not separated.

The earlier bond-energy term values for the Si–C bond, derived from the heat of formation of carborundum, are given by Pauling (*op. cit.*) as 57·6, by Sidgwick (" The Chemical Elements and Their Compounds," Oxford Univ. Press, 1950, p. 556) as 69·1, and by Paul (" Principles of Chemical Thermodynamics," McGraw-Hill, 1951, p. 146) as 143·2 kcal./mole; it is likely that the value intended by Paul is half that given, namely 71·6 kcal./mole. Rochow (" An Introduction to the Chemistry of the Silicones," Chapman and Hall, 2nd edn., 1951, p. 19) considers that since the melting temperature of carborundum (*ca.* 2700°) is lower than the sublimation temperature of carbon (*ca.* 3500°) the Si–C must be considerably weaker than the C–C bond. Since the usually accepted value for the latter is about 83 on the basis of the 171·7 kcal./mole value for the heat of atomisation of carbon (Coates and Sutton, *J.*, 1948, 1187, give 83·0 kcal./mole), the present value of 64 kcal./mole is in conformity with such a view; so are the value derived from the heats given in the " Selected Values, etc." (71·8 kcal./mole) and Sidgwick's value of 69·1 compared with his 81·6 for the C–C bond-energy term, although it should be noted that the heat of formation ($\Delta Hf°$) of SiC is quoted by Sidgwick as −57·6 against the usual value of −27·6 kcal./mole (" Selected Values, etc."). Energy terms derived from silica for the Si–O bond are listed by both Pauling and Sidgwick as 89·3, by Syrkin and Dyatkina (" Structure of Molecules," Butterworth, 1950, p. 260) as 89 kcal./mole, and by Paul (*op. cit.*) as 104 kcal./mole. A value of 103·8 is calculated from the data of " Selected Values, etc." and $\Delta Hf°$ for amorphous silica = −208·14. The reason for Pauling's choice of 89·3 is not apparent from his text; the figure, which may possibly involve an arithmetical error, is quoted extensively in the literature.

The energy terms obtained in the present work for the Si–C and Si–O bonds are thus lower and higher, respectively, than those calculated from the data in " Selected Values, etc." A degree of ionic character of 50% is assigned by Pauling to the Si–O linkage; Sauer and Mead (*J. Amer. Chem. Soc.*, 1946, **68**, 1794) assess the value at 37%. Both quote a 12% ionic character for the Si–C linkage. But it is well known (*e.g.*, Rochow, *op. cit.*) that the polarity of the Si–C bond is reduced by the addition of positive substituents to the carbon and negative to the oxygen atom; this will be the case with the polydimethylsiloxanes, hydrogen and oxygen being the respective substituents, and it is not unreasonable to suppose that the Si–O and Si–C bond-energy terms will be respectively stronger and weaker in the methylsiloxanes than in those compounds containing homogeneous bonds. It is not suggested that the present bond-energy terms are necessarily superior to those derived from the heats of combustion of silicon and carborundum, or that they should supersede the earlier ones for all purposes; but the new values should be more appropriately applicable to many organo-silicon compounds, and it is of interest to compare them with the few observed heats of formation of members of this class. Results so obtained are given in Table 5.

The values given in col. (i) have been recalculated from the combustion data of Tanaka *et al.* (*loc. cit.*) on the basis of the more recent heat of formation of silica (−208·14 instead of −203·34 kcal./mole). Bond-energy terms, in addition to those for Si–C and Si–O, employed in the calculation of the heats of formation of col. (iii) were as used by Coates

TABLE 5.

	$\Delta Hf°$, in kcal./mole.			
Compound	(i) Obs. by Tanaka *et al.*	(ii) Calc. by Tanaka *et al.*	(iii) Calc. from Me siloxanes	(iv) Calc. from SiC & SiO_2
1. $(Me_2SiO)_3$	−369·1	−353·5	−463	−431
2. $(Ph_2SiO)_3$	−232·6	−139	−216	−184
3. $Et_2Si(OH)_2$	−222·8	−193·6	−228	−217
4. $Me_2Si(OEt)_2$	−199·8	−174	−214	−203
5. $Pr^n_2Si(OEt)_2$	−241·2	−203·6	−233	−222

and Sutton (" *B* " values, *loc. cit.*); C–H, 98·5 (derived from the CH_2 group of the higher paraffins); O–H, 110; C–O, 85·5; C–C, 83·0; C=C, 146·5; and 36 kcal./mole for the resonance energy of the benzene ring. The figures of col. (iv) differ from those of (iii) only in that the Si–C and Si–O energy terms employed were those derived from carborundum and silica. Latent heats of evaporation used for cols. (iii) and (iv) were calculated by Trouton's rule, values of 9 being taken for the first four compounds and 11 kcal./mole for the fifth; since the first three compounds are solid at 25°, latent heat of fusion is involved, and a value of 4 kcal./mole has arbitrarily been taken in each case.

From the $\Delta Hf°$ values of the last three compounds of Table 5 it will be seen that, as far as agreement between those observed and calculated is concerned, there is little to choose between cols. (iii) and (iv); the values in each case are closer to the observed than are those of col. (ii). The calculated and observed values for the heat of formation of hexamethyl*cyclo*trisiloxane (D_3) given in the original paper of Tanaka *et al.* agreed with each other to within 1%; such close agreement was purely accidental, for (*a*) the $\Delta Hf°$ values for SiO_2 then available have since been shown to be incorrect (Humphrey and King, *loc. cit.*) and (*b*) the Si–O bond-energy term listed by Pauling is erroneous. Employing the present data for the Si–O and Si–C bond-energy terms, derived from the polydimethylsiloxanes or otherwise, we see that the calculated values of $\Delta Hf°$ for D_3 differ from the observed by at least −60 kcal./mole. It is not altogether apparent why there should be this large discrepancy, unless it be that strain energy considerably affects the true heat of formation (Pauling and Simonetta, *J. Chem. Phys.*, 1952, **20**, 29, report that the strain energy connected with the distortion of each of the three C–C–C bond angles in *cyclo*propane to 60° is 22 kcal./mole). Frevel and Hunter (*J. Amer. Chem. Soc.*, 1945, **67**, 2275) have found the hexamethyl*cyclo*trisiloxane ring to possess an essentially planar configuration, yet the Si–O–Si bond angle of hexamethyldisiloxane (M_2) has been claimed

from dipole-moment evidence (Sauer and Mead, *loc. cit.*) to be 160° ± 15°, and 140° from electron-diffraction measurements (Rochow, *op. cit.*, quoting a personal communication from Lucht and Harker). If this angle were maintained in D_3, an unusually acute O–Si–O angle of 80° ± 15°, or 100°, would result. The angles within the ring are, in fact, known to be: Si–O–Si, 125° ± 5°; O–Si–O, 115° ± 5° (Sutton and Allen, *Acta Cryst.*, 1950, **3**, 60, quoting a personal communication from Weller and Bauer). Increments in $\Delta Hf°$ for the D unit are calculated from the polydimethylsiloxanes to be −153 kcal./mole, whereas $\frac{1}{3}[\Delta Hf°(Me_2SiO)_3 - \text{Latent heat}] = -122$ kcal./mole; such a discrepancy is well outside the limits of experimental error. It is of interest that the infra-red absorption peak assigned to the Si–O stretching vibration is at 1020 cm.$^{-1}$ in the case of D_3, whereas in D_4 and the higher cyclic members the peak is at about 1080 cm.$^{-1}$ (Richards and Thompson, *J.*, 1949, 124). The calculated heat of formation of hexaphenyl*cyclo*trisiloxane [col. (iii)], while considerably closer to the observed value than is that of Tanaka *et al.*, is still about 16 kcal./mole lower than the experimental value. In addition to the uncertainty of strain-energy contributions, unreliability of any calculated value for the heat of formation arises from the facts that the result is the difference between two large numbers, and that the resonance-energy contribution of the six benzene rings is not known accurately; but it is possible that the effect of aryl carbon atoms attached to silicon will be to alleviate much of the strain (Freiser, Charles, Speier, and Eagle, *J. Amer. Chem. Soc.*, 1951, **73**, 5229), although Roth (*ibid.*, 1947, **69**, 474) considers the O–Si–O angle to be " soft " even when two methyl groups are attached to the silicon.

The heat of formation of tetraethyl orthosilicate is listed in " Selected Values, etc." as $\Delta Hf° = -318$ kcal./mole; this value had been calculated from Ogier's original measurements of the heat of hydrolysis of the ester (*loc. cit.*). Ogier had found the hydrolysis to be instantaneous and the maximum temperature rise to be attained in 5 min.; it is now known that the ethyl ester does not react immediately with pure water, but does so if the pH of the solution is sufficiently low or if another substance such as ethanol is present, *inter alia*, to increase the mutual solubility of the reactants. The boiling point of the ester is given by Ogier as 165° (cf. 168·55° ± 0·05°, Solana and Moles, *Anal. real. Soc. esp. Fis. Quim.*, 1932, **30**, 886) and it is possible that a trace of impurity served to expedite hydrolysis. His value of $\Delta H = -21{\cdot}6$ kcal./mole for the heat of hydrolysis compares favourably with a preliminary value of $\Delta H = -18{\cdot}0$ kcal./mole obtained by the author for immediate hydrolysis in 0·1N-hydrochloric acid. A value of 10 kcal./mole being used for the latent heat of evaporation of the ester (*idem, ibid.*), $\Delta Hf°$ of tetraethyl orthosilicate is calculated on the 104 kcal./mole Si–O value to be −330, and on the 117 value to be −382 kcal./mole. It is of interest that the observed value lies much closer to that calculated on Si–O bond-energy terms derived from a purely inorganic compound than to that derived from organosilicon compounds containing carbon attached directly to silicon.

As is the case with many classes of compound, it seems that calculations of heats of formation of the silicones should employ bond-energy terms derived from compounds of a closely similar nature to those to which they are applied.

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393. *Reactions of Methazonic Acid. Part III.* A Novel Reaction of 3-Aminolepidine.*

By D. W. Ockenden and K. Schofield.

3-Aminolepidine reacted with two mols. of nitrous acid to give 1 : 2 : 3 : 9-tetra-azaphenanthrene 3-oxide, converted by acid into 3-azidoquinoline-4-aldehyde. The latter when heated gave quinolino(3′ : 4′-3 : 4)sydnone. Diazotisation of the amine in dilute acid produced some 3*H*-1 : 2 : 6-triaza-4 : 5-benzindene.† In concentrated hydrochloric acid the initial reaction between 3-aminolepidine and nitrous acid produced a deep violet colour, not observed in sulphuric acid of similar concentration. 3-Amino-6-chlorolepidine gave similar reactions.

The *N*-nitroso-derivative of 3-acetamidolepidine was converted by hot benzene into 3*H*-1 : 2 : 6-triaza-4 : 5-benzindene.

Various ultra-violet absorption spectra are recorded.

Recently, Schofield and Theobald (*J.*, 1950, 395) described the diazotisation of 3-aminolepidine (I; R = H) and the coupling of the diazonium salt with pyridine. The diazotisation in concentrated hydrochloric acid gave a violet diazonium solution, and the reaction was stated to be complicated. In contrast, Eiter and Nagy (*Sitzungsber. Oesterr. Akad. Wiss.*, Abt., II*b*, 1949, **158**, 607), who diazotised the amine in 2N-sulphuric acid, evidently did not observe a violet diazonium solution, and isolated the alkali-soluble triazabenzindene (II; R = H), m. p. 224°. We now present the results of a re-examination of this diazotisation.

Both Eiter and Nagy and Schofield and Theobald prepared 3-aminolepidine by reducing the nitro-compound, obtained from *o*-aminoacetophenone and methazonic acid, with stannous chloride, but whereas the former authors isolated the amine as a hemihydrate, m. p. 90—91° after melting at 40° and re-solidifying, the latter described a hydrate, m. p. 72—73°. It was therefore necessary to establish that these different workers had the same compound in hand. Repetition of the reduction as described by the Austrian authors gave an amine, m. p. 96—98°, but this was converted into the monohydrate, m. p. 72—73° by crystallisation from aqueous ethanol (Eiter and Nagy used ether–light petroleum). Catalytic reduction of 3-nitrolepidine in methanol, with palladium–charcoal, gave a high yield of an amine which at first behaved like that of Eiter and Nagy, but when crystallised and seeded also gave the monohydrate. It is clear therefore that the amines previously reported differed only in their degree of hydration.

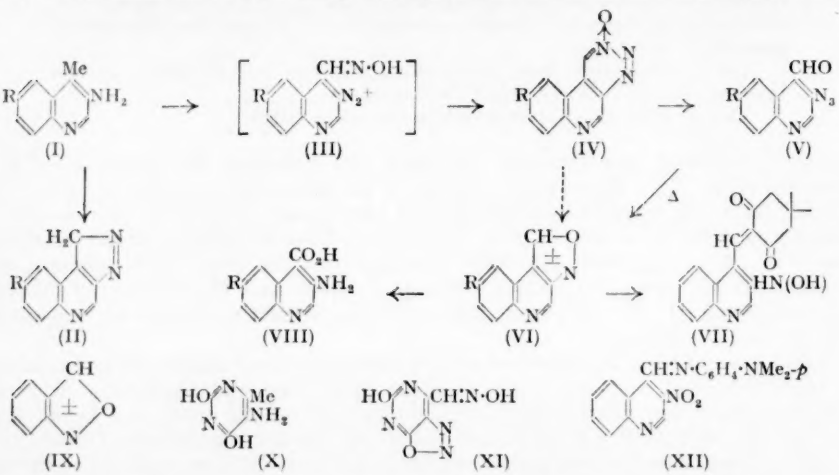
Schofield and Theobald (*loc. cit.*) noticed that the violet solution formed by diazotising 3-aminolepidine in concentrated hydrochloric acid rapidly deposited a brown solid (A). In repeating this work we were unable to improve the low yields of 3-pyridyl-lepidines obtained by the method previously described, and found (A) to be the major product of the diazotisation, its formation being accompanied by fading of the violet colour of the solution. If (A) was left in contact with the acid solution from which it had separated it slowly dissolved, and in our first experiment by basification of the resulting solution a new substance (C) was isolated. Subsequently, this result could not be reproduced, basification of the solution produced by dissolution of (A) always providing a different compound (B). (C) was a base, m. p. 117—118°, for which analysis indicated the formula $C_{10}H_6ON_2$, or, less likely, $C_{10}H_8ON_2$. The latter would correspond to 3-aminoquinoline-4-aldehyde, whilst the most obvious structure with the former composition would be the quinolino*iso*-oxazole (VI; R = H). That the latter is the correct structure is proved by the following facts. The compound could not be acetylated or benzoylated, but with nitrous acid it gave a diazonium solution capable of coupling with β-naphthol; with dimedone it did not give the usual type of aldehyde derivative, but the additive compound (VII; R = H); warm dilute alkali converted (C) into 3-aminocinchoninic acid (VIII; R = H). Analogies for each of these reactions are available in the behaviour of anthranil (IX) (Morton, " The

* Part II, *J.*, 1950, 395.

† See footnote on p. 1918.

Chemistry of Heterocyclic Compounds," McGraw-Hill, New York, 1946, pp. 425 *et seq.*). Although a compound of this type does not appear to have been treated with dimedone before, anthranil undergoes a similar addition reaction with another carbonyl reagent, *viz.*, hydroxylamine (*op. cit.*).

The substance (B), $C_{10}H_6ON_4$, was basic and melted with decomposition at 135°; when cooled, the melt solidified and then had m. p. 117—118°. It seemed likely that (B) lost nitrogen at its m. p., being converted into (C). This was proved by the fact that the conversion could be effected by boiling a solution of (B) in dioxan, the method finally adopted for preparing (C). These facts suggested that (B) was 3-azidoquinoline-4-aldehyde (V; R = H), a deduction supported by the preparation of the 2 : 4-dinitrophenylhydrazone.



The parent compound (A), being insoluble in most solvents, was difficult to purify. Early and unreproducible attempts to crystallise it from acetic acid or dioxan merely produced (C), with the liberation of nitrogen, but after crystallisation [m. p. 216° (decomp.)] from pyridine, it was found to be isomeric with (B). The only possible structure for (A) is that of the tetra-azaphenanthrene 3-oxide (IV; R = H). This attribution would imply that 2 mols. of nitrous acid react initially with 3-aminolepidine, and support is given to this by the formation of (A) in almost quantitative yield by the use of this quantity of reagent.

The reaction with nitrous acid of the methyl group in 3-diazolepidine was unexpected, such reactions, though common with the analogously activated groups in methyl ketones, being rare in heterocyclic systems. 5-Amino-6-methyluracil (X) gives with nitrous acid the oxime (XI) (Rose, *J.*, 1952, 3448), and the 2-methyl group of 2 : 3 : 3-trimethylindolenine is similarly nitrosated (Plancher, *Ber.*, 1898, **31**, 1496). 3-Aminoquinaldine, on the other hand, appears to be diazotised normally (Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 626; Bargellini and Berlingozzi, *Gazzetta*, 1923, **53**, 3), although the description given by Stark and Hoffmann (*Ber.*, 1913, **46**, 2697) suggests that this case might deserve re-examination. 3-Nitrolepidine did not react with nitrous acid.

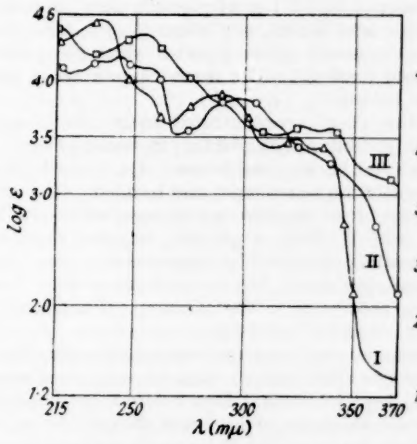
The precursor of (IV; R = H) must be the oxime (III; R = H), and the sequence (III ⟶ IV ⟶ V ⟶ VI) closely parallels that occurring when *o*-aminoaceto- or *o*-aminobenzo-phenone oxime is diazotised (Meisenheimer, Senn, and Zimmermann, *Ber.*, 1927, **60**, 1736).

The intense violet colour of the solution formed immediately upon diazotisation of 3-aminolepidine in concentrated hydrochloric acid remains unexplained. Experiment showed that in N- or 2N-hydrochloric acid the diazonium solution was pale yellow, and the precipitate of (IV; R = H) redissolved either very slowly or not at all at these acid concentrations. With 5N-acid the solution was dark orange and deposited no solid. At 6N

the colour was dark red, and at greater concentrations violet, these solutions all depositing (IV; R = H), which was slowly redissolved, as described. By carrying out diazotisations in solutions ranging from N- to 8N-hydrochloric acid and leaving the precipitated solid in contact with the mother-liquors overnight, it was possible to collect undissolved (IV; R = H) in amounts which decreased as acid concentration increased, and by basifying the mother-liquors to isolate (V; R = H), except with N-hydrochloric acid, in which case the triazabenzindene (II; R = H) was obtained.

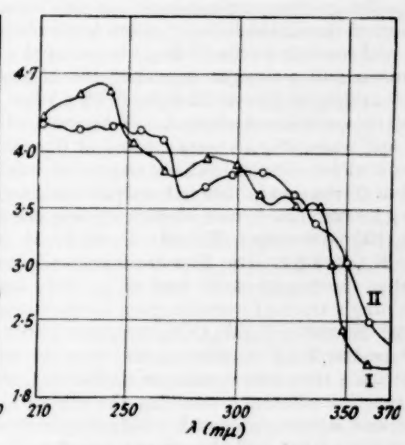
Although we could not isolate (II; R = H) in the way described by Eiter and Nagy (*loc. cit.*), the substance was obtained by diazotising the amine in N-sulphuric acid and, after removal of the small amount of (IV; R = H) still remaining after 12 hours, neutralising the solution. Again the use of more concentrated acid facilitated the transformation of (IV; R = H), and from 5N- and 8N-sulphuric acid the triazabenzindene (II; R = H) was contaminated with 3-azidoquinoline-4-aldehyde. The diazonium solution in N-sulphuric acid was yellow, and light orange and orange respectively in 5N- and 8N-acid. Violet solutions were not encountered when sulphuric acid was used.

FIG. 1.



(I) 3H-1 : 2 : 6-*Triaza*-4 : 5-*benzindene*.
(II) *Quinolino*(3′ : 4′-3 : 4)*isooxazole*.
(III) 3-*Azidoquinoline*-4-*aldehyde*.
(*In absolute alcohol.*)

FIG. 2.



(I) 2′-*Chloro*-3H-1 : 2 : 6-*triaza*-4 : 5-*benzindene*.
(II) 6′-*Chloroquinolino*(3′ : 4′-3 : 4)*isooxazole*.
(*In absolute alcohol.*)

Roughly similar observations were made with 3-amino-6-chlorolepidine (I; R = Cl) (Schofield and Theobald, *loc. cit.*). On diazotisation in both 2N-hydrochloric acid and -sulphuric acid, (IV; R = Cl) was precipitated, and from the reaction solution the chlorotriazabenzindene (II; R = Cl) was isolated. Again the use of 2 mols. of sodium nitrite gave (IV; R = Cl) in superior yield. The diazonium solutions in these cases were pale yellow, and even in concentrated hydrochloric acid became only light orange. In this last case the *N*-oxide (IV; R = Cl) redissolved when left in contact with the reaction solution, and the base (VI; R = Cl) was isolated on neutralisation. In this series the azide was not encountered. The quinolino*iso*oxazole (VI; R = Cl) was characterised by conversion into 3-amino-6-chlorocinchoninic acid (VIII; R = Cl).

Recently, Adams and Hey (*J.*, 1951, 1521) converted 3-acetamido-1 : 2-dimethyl-4-quinolone into 1-methylpyrazolo(4′ : 5′-2 : 3)-4-quinolone by heating its *N*-nitroso-derivative in benzene. Similarly we converted 3-acetamidolepidine by means of nitrosyl chloride in acetic anhydride into the *N*-nitroso-derivative, and transformed the latter into (II; R = H) identical with the compound described above. We were unable to prepare the *N*-nitroso-derivative of 3-acetamido-6-chlorolepidine.

The ultra-violet absorption spectra of (II; R = H and Cl), (VI; R = H and Cl), and

(V; R = H) are recorded in Figs. 1 and 2. The spectra of the analogous compounds are clearly similar, but the chlorine atom produces a bathochromic shift.

Early in this work we prepared the anil (XII) from 3-nitrolepidine and *p*-nitrosodimethylaniline, as a possible source of 3-nitroquinoline-4-aldehyde.

Experimental

3-Aminolepidine.—3-Nitrolepidine (0·5 g.), palladium–charcoal (0·2 g.), and methanol (100 c.c.) were shaken with hydrogen. Reduction was complete in 120 min., and filtration and concentration gave the amine (0·48 g.), melting like that described by Eiter and Nagy (*loc. cit.*). Recrystallisation from aqueous alcohol, with seeding, gave the monohydrate, m. p. 72—73°.

1 : 2 : 3 : 9-Tetra-azaphenanthrene 3-Oxide.—3-Aminolepidine (0·25 g.) in concentrated hydrochloric acid (25 c.c.) and water (10 c.c.) was treated at 0° with sodium nitrite (0·25 g.) in water (2 c.c.). The product [0·26 g., 84%; m. p. 205° (decomp.)] began to separate immediately and was collected when the violet colour had faded (about 5 min.). The *3-oxide* formed small, dark brown crystals, m. p. 216° (decomp.) (Found: C, 61·3; H, 3·3; N, 27·8. $C_{10}H_6ON_4$ requires C, 60·6; H, 3·1; N, 28·3%), from pyridine.

With the amine (2·0 g.), concentrated hydrochloric acid (20 c.c.), water (18 c.c.), and sodium nitrite (0·9 g.) the purple colour was also developed and 1·1 g. of product were obtained. A solution of the amine (0·2 g.), dilute hydrochloric acid (5 c.c.), and water (5 c.c.), when treated at 0° with sodium nitrite (0·09 g.) in water (1 c.c.), gave a yellow solution which slowly became red-brown and overnight deposited the *N*-oxide (0·09 g.). The mother-liquor when basified gave 3-azidoquinoline-4-aldehyde (0·02 g.) (see below).

3-Azidoquinoline-4-aldehyde.—3-Aminolepidine (1 g.), concentrated hydrochloric acid (10 c.c.), and water (5 c.c.) were treated at 0° with sodium nitrite (0·45 g.) in water (5 c.c.). The initially violet solution quickly deposited solid and became red-brown. On being kept overnight at 0° the precipitate redissolved, and the solution was filtered and basified. The product (0·75 g.) crystallised from acetone, giving orange-brown needles of *3-azidoquinoline-4-aldehyde*, m. p. 135° (decomp.) (Found: C, 60·3; H, 3·1; N, 28·6. $C_{10}H_6ON_4$ requires C, 60·6; H, 3·0; N, 28·3%). Its *2 : 4-dinitrophenylhydrazone* exhibited polymorphism: as obtained initially, the orange solid had m. p. 255—260° (decomp.), but crystallisation from benzene containing a trace of pyridine gave small orange needles, m. p. 160° (decomp.) (Found: C, 51·3; H, 2·9; N, 28·6. $C_{16}H_{10}O_4N_8$ requires C, 50·8; H, 2·7; N, 29·6%).

Quinolino(3′ : 4′-3 : 4)isooxazole.—On one occasion only was this compound isolated instead of the azide from an experiment similar to that described above; subsequently, even when the acid reaction solution containing the azide was kept for several days before being basified, the azide was always recovered. 3-Azidoquinoline-4-aldehyde (0·6 g.) and dioxan (30 c.c.) were refluxed for 4 hr., and the solvent was then removed *in vacuo*. The residue when crystallised from aqueous alcohol gave *quinolino(3′ : 4′-3 : 4)isooxazole* (0·35 g.), fawn-coloured leaflets, m. p. 117—118° (Found: C, 70·2; H, 3·4; N, 16·9. $C_{10}H_6ON_2$ requires C, 70·6; H, 3·6; N, 16·5%). The *iso*oxazole and dimedone in aqueous ethanol gave a derivative, *4-(2 : 6-diketo-4 : 4-dimethylcyclohexylidenemethyl)-3-hydroxyaminoquinoline*, which crystallised from the same solvent in orange leaflets, m. p. 145—146° (Found: C, 69·7; H, 5·8; N, 8·6. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

3-Aminocinchoninic Acid.—The *iso*oxazole (0·03 g.) and 2N-sodium hydroxide (3 c.c.) were kept at 95° for 2 hr. The resulting clear yellow solution was made faintly acid (Congo-red) with sulphuric acid (2N), one drop of ammonia added, and the solution slowly evaporated. Orange-yellow needles [0·02 g.; m. p. 230° (decomp.)] separated which gave no mixed m. p. depression with authentic 3-aminocinchoninic acid.

3-Aminocinchoninic acid was first obtained by Colonna (*Boll. sci. Fac. Ind. Bologna*, 1941, 89) who reduced 3-nitrocinchoninic acid with iron and acetic acid. We found this procedure very inconvenient and obtained the amine as follows. 3-Nitrocinchoninic acid (1 g.), water (80 c.c.), sodium hydroxide (0·2 g.), and palladium–charcoal (0·25 g.) were shaken with hydrogen. Reduction was complete in 1 hr. and the filtered solution was concentrated to half volume. Careful neutralisation with 2N-sulphuric acid precipitated 3-aminocinchoninic acid (0·86 g., 100%), m. p. 230—232° (decomp.).

*3H-1 : 2 : 6-Triaza-4 : 5-benzindene.**—(i) 3-Aminolepidine (0·5 g.) in sulphuric acid (10 c.c.; 2N) was diazotised at 0° with sodium nitrite (0·25 g.) in water (2 c.c.). From the pale

* The symbol 3*H* indicates the position of the " indicated " (" extra ") hydrogen atom as in (II), but we do not wish to be committed to this particular location of this atom.

yellow diazonium solution a solid separated, and after the addition of iced water (10 c.c.) it (tetrazaphenanthrene oxide, 0·13 g.) was collected. The filtrate was basified with ammonia and the precipitate (0·33 g.; m. p. 210—212°) was crystallised from benzene–pyridine. 3*H*-1 : 2 : 6-Triaza-4 : 5-benzindene formed small fawn-coloured crystals, m. p. 219—220° (Found: C, 71·8; H, 4·5; N, 23·8. Calc. for $C_{10}H_7N_3$: C, 71·0; H, 4·4; N, 24·8%). Eiter and Nagy (*loc. cit.*) gave m. p. 224°.

(ii) When 3-aminolepidine (0·5 g.) and acetic anhydride (10 c.c.) were kept at 95% for 1 hr., and the solvent was then removed, 3-acetamidolepidine (0·6 g.; m. p. 200—204°) suitable for further use was obtained. Eiter and Nagy (*loc. cit.*) gave m. p. 206°. The amide (0·2 g.), acetic acid (2 c.c.), acetic anhydride (1 c.c.), anhydrous potassium acetate (0·1 g.), and phosphoric oxide (0·05 g.) were treated at 0° with nitrosyl chloride (0·2 c.c.) in acetic anhydride (0·8 c.c.). The mixture was kept at 0° for 1 hr., with occasional shaking, poured on ice, and basified with sodium carbonate solution. The greenish gum which separated was taken up in benzene and the dry (Na_2SO_4) extract was refluxed for 3 hr. By concentration (charcoal) of the filtered solution the triazabenzindene (0·11 g.) was obtained, having m. p. 218—220° alone and mixed with the compound above.

6-*Chloro*-1 : 2 : 3 : 9-*tetra-azaphenanthrene* 3-*Oxide*.—The hydrochloride suspension from 3-amino-6-chlorolepidine (1 g.), concentrated hydrochloric acid (10 c.c.) and water (5 c.c.) was treated at 0° with sodium nitrite (0·8 g.) in water (5 c.c.). The solution became yellow, then orange-red, and deposited a pale yellow solid. Iced water (25 c.c.) was added, and after 12 hr. at 0° the precipitate [1·14 g.; m. p. 180—185° (decomp.)] was collected. 6-*Chloro*-1 : 2 : 3 : 9-*tetra-azaphenanthrene* 3-*oxide* crystallised from benzene containing a trace of pyridine as light brown prisms, m. p. 220° (decomp.) (Found: C, 52·1; H, 2·6; N, 21·1. $C_{10}H_5ON_4Cl$ requires C, 51·6; H, 2·2; N, 24·1%). This may be impure (cf. analysis) but its structure is not in doubt.

6′-*Chloroquinolino*(3′ : 4′-3 : 4)iso*oxazole*.—Although this compound was formed when 3-amino-6-chlorolepidine was diazotised in concentrated hydrochloric acid and the initial precipitate was allowed to redissolve overnight in the reaction liquor, the sydnone was best prepared as follows. The pure chloro-oxide (0·5 g.) and concentrated hydrochloric acid (20 c.c.) were left together for 12 hr., and the resulting solution was basified with ammonia. The precipitate (0·43 g.) gave yellow needles of 6′-*chloroquinolino*(3′ : 4′-3 : 4)iso*oxazole*, m. p. 202—204° (Found: C, 58·7; H, 2·8; N, 14·3. $C_{10}H_5ON_2Cl$ requires C, 58·7; H, 2·5; N, 13·7%), from benzene–light petroleum (b. p. 60—80°).

The chloro-*iso*oxazole (0·1 g.) was converted by aqueous sodium hydroxide by the method previously described into 3-*amino*-6-*chlorocinchoninic acid* (0·1 g.), small yellow flakes, m. p. 263—264° (decomp.) (Found: C, 54·7; H, 3·4. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·2%), from alcohol.

2′-*Chloro*-3H-1 : 2 : 6-*triaza*-4 : 5-*benzindene*.—The hydrochloride suspension from 3-amino-6-chlorolepidine (0·2 g.) and hydrochloric acid (5 c.c.; 2N) was treated at 0° with sodium nitrite (0·08 g.) in water (1 c.c.). The solution, yellow at first, became orange and deposited a solid. Iced water (5 c.c.) was added, and after 12 hr. at 0° the *N*-oxide (0·11 g.) was removed. Basification of the mother-liquor gave the *chlorotriazabenzindene* (0·1 g.); it separated from benzene–pyridine as small, lemon-yellow needles, m. p. 283—285° (Found: C, 58·8; H, 3·0. $C_{10}H_6N_3Cl$ requires C, 58·9; H, 3·0%). A similar experiment in sulphuric acid (5 c.c.; 2N) gave the *N*-oxide (0·18 g.) and very impure chlorotriazabenzindene (0·02 g.).

3-*Acetamido*-6-*chlorolepidine*.—Prepared as described for 3-acetamidolepidine, this *compound* gave small needles, m. p. 233—235° (Found: C, 61·2; H, 4·4. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 4·7%), from dilute alcohol.

Reaction of 3-*Nitrolepidine with* p-*Nitrosodimethylaniline*.—3-Nitrolepidine (0·3 g.), *p*-nitrosodimethylaniline (0·24 g., 1 mol.), and anhydrous sodium carbonate (0·03 g.) were refluxed in alcohol (20 c.c.) for 8 hr. The brown solution was concentrated, and the product (0·12 g.; m. p. 146—156°) collected. The *anil* crystallised from alcohol as small grey-black crystals, m. p. 155—157° (Found: C, 67·2; H, 4·8. $C_{18}H_{16}O_2N_4$ requires C, 67·5; H, 5·0%).

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394. *Interaction of Phosphorus Trichloride with Alcohols and with Hydroxy-esters.*

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Phosphorus trichloride is used both for the replacement of hydroxyl by chlorine and for the formation of esters of phosphorus; these two functions are correlated, and the sequence of reactions is studied. Addition of an alcohol such as *n*-butyl alcohol to the trichloride leads to rapid stepwise alkoxylation of phosphorus, followed by dealkylation of the trialkyl phosphite to dialkyl hydrogen phosphite. Yields of the last, dichloridite, $PCl_2{\cdot}OR$, and chloridite, $PCl(OR)_2$, depend mainly on the relative amount of alcohol added. Most of the alkyl chloride is formed during the first few minutes, and is mainly due to dealkylation (one group) of the trialkyl phosphite by means of hydrogen chloride. Later, the dialkyl hydrogen phosphite, the chloridite, and to a much less degree the dichloridite are dealkylated.

The ethyl esters of glycollic, β-hydroxypropionic, and malic acids behaved as does *n*-butyl alcohol. Esters could not be isolated by the interaction of *tert.*-butyl alcohol and the trichloride alone, owing to the rapid formation of alkyl chloride and phosphorous acid, but in the presence of pyridine the dialkyl hydrogen phosphite was obtained.

Phosphorus trichloride is used both for the preparation of esters containing phosphorus (Railton, *J.*, 1854, **7**, 216; Wichelhaus, *Annalen*, 1868, Suppl. **6**, 257; Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687; Milobendzki and Sachnowski, *Chem. Polski*, 1917, **15**, 34; Gerrard, *J.*, 1940, 1464; 1944, 85; McCombie, Saunders, and Stacey, *J.*, 1945, 380; Kosolopoff, "Organophosphorus Compounds," Wiley, New York, 1950) and for the replacement of hydroxyl by chlorine (cf. Clark and Streight, *Proc. Roy. Soc. Canada*, 1929, **23**, 77; Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, **26**, 451). Trichloride–alcohol systems are considered from both these aspects, and the following description applies to hydroxy-compounds which behave similarly to *n*-butyl alcohol.

During the dropwise addition of the alcohol to the trichloride at about 0° there is a quick, stepwise alkoxylation of phosphorus:

$$(1)\quad R{\cdot}OH + PCl_3 \longrightarrow \underset{\text{Alkyl phosphorodichloridite}}{PCl_2{\cdot}OR} + HCl$$

$$(2)\quad R{\cdot}OH + PCl_2{\cdot}OR \longrightarrow \underset{\text{Dialkyl phosphorochloridite}}{PCl(OR)_2} + HCl$$

$$(3)\quad R{\cdot}OH + PCl(OR)_2 \longrightarrow P(OR)_3 + HCl$$

By the time the alcohol (1 mol.) has been added to the trichloride (1 mol.), in addition to the main product (dichloridite), the chloridite and even some tri-ester have been formed, and a corresponding amount of trichloride remains. The trialkyl phosphite is readily dealkylated (1 group) by hydrogen chloride (reaction 4) (cf. Gerrard and Whitbread, *J.*, 1952, 914), and this is an irreversible reaction belonging to a different sequence; for dealkylation can proceed through the second step (slow) and even through the extremely slow third step:

$$(4)\quad P(OR)_3 + HCl \longrightarrow P(OH)(OR)_2 + RCl$$

$$(5)\quad P(OH)(OR)_2 + HCl \longrightarrow P(OH)_2(OR) + RCl, \text{ etc.}$$

By stopping the addition of alcohol before 1 mol. has been added, a good yield of dichloridite can be obtained, but chloridite and hydrogen phosphite are also formed. At the 2-mol. stage the yield of chloridite has increased, but so has that of hydrogen phosphite, and it is difficult to get a pure specimen of chloridite from this mixture. The third mol. of alcohol completes the alkoxylation of the phosphorus and produces dialkyl hydrogen phosphite and alkyl chloride in fair agreement with equation (6):

$$(6)\quad 3ROH + PCl_3 \longrightarrow P(OH)(OR)_2 + RCl + 2HCl$$

This is the standard procedure for the preparation of hydrogen phosphites; but to increase the yield of alkyl chloride beyond 33% requires longer times and higher temperatures and, to convert all the halogen into alkyl chloride, hydrogen chloride must be conserved.

The dealkylation of *n*-butyl phosphorodichloridite by hydrogen chloride was slow at 17°, but quicker at 65°, and there was no indication that the dichloridite can itself give alkyl chloride even on being heated. The chloridite was more quickly dealkylated than the dichloridite at 17°, and at 65° it was completely so after 48 hours. The conclusion is that for the $3ROH + PCl_3$ system the reaction which is almost entirely responsible for the formation of alkyl chloride in the first few minutes is the dealkylation of the trialkyl phosphite to dialkyl hydrogen phosphite. Longer reaction times would allow the dealkylation of the latter to proceed, but there are no chloro-esters in the system to make any contribution. In the systems $2ROH + PCl_3$ and $ROH + PCl_3$, the alcohol being added to the trichloride, the amount of alkyl chloride quickly formed will be less than in the previous system, because complete alkoxylation of all the phosphorus cannot occur. The slow dealkylation of the chloro-esters, however, can give some alkyl chloride.

To determine the maximum loss (expressed as yield % of alkyl chloride) of easily hydrolysable chlorine without unproductive loss of hydrogen chloride, reagents were allowed to react in sealed tubes. At 18° there was a comparatively small increase in yield of alkyl chloride when the reaction time was extended from 24 to 72 hours. In the alcohol–trichloride system (Table 1), the yield of alkyl chloride was greatest for the ratio $3ROH : PCl_3$, and even then only about 50% of the chlorine was converted into alkyl chloride. As the proportion of trichloride was increased, so the yield of alkyl chloride decreased. In pentane and benzene, as solvents, the yield of alkyl chloride was not more than about 33% for the 3 : 1 ratio, although for the ratio $ROH : PCl_3$ the yield was the same as when no solvent was used. It is supposed that the solvent in some way hinders the dealkylation of the hydrogen phosphite, and this effect is particularly noticeable with ether. Data in Table 2 show that in the alcohol–dichloridite system, the ratio being $\lessdot 2ROH : PCl_2{\cdot}OR$, about 50% of the chlorine was converted, and this is in accord with equations (2), (3), and (4). As the proportion of the dichloridite was increased to 1 : 1, the yield of alkyl chloride decreased, because not all the dichloridite could be converted into tri-ester. Solvents again had the effect mentioned.

In the chloridite–alcohol system (Table 3), any proportion of alcohol greater than $R{\cdot}OH : PCl(OR)_2$ can effect complete dechlorination, and therefore lead to a complete removal of easily hydrolysable chlorine by the reaction $R{\cdot}OH + PCl(OR)_2 \longrightarrow RCl + P(OH)(OR)_2$. That only 90% of complete removal was quickly achieved is attributed to the withholding of hydrogen chloride either by the excess of alcohol, when this was used, or by the hydrogen phosphite, a known property of these compounds.

Table 4 contains data from a series of experiments in which the reaction mixtures were analysed after shorter time intervals. The speed of removal of the last chlorine atom and of the first dealkylation reaction is amply illustrated by the fact that within 2 minutes of mixing of the alcohol (1 mol.) with the chloridite (1 mol.) 90% of the chlorine had been converted into alkyl chloride.

To prepare di-*n*-butyl phosphorochloridite (required for the preparation of mixed phosphites) in good yield, an attempt was made to hinder loss of the third chlorine atom by a mass-law effect, by using alcohol saturated with hydrogen chloride for addition either to the trichloride or to the dichloridite, a procedure which had been found very effective in the thionyl chloride system (unpublished work). This, however, failed. The method found most convenient (60% yields) was the addition of an ethereal solution of alcohol (1 mol.) and pyridine (1 mol.) to the dichloridite (1 mol.) in ether.

A complete description of phosphorus trichloride–alcohol systems must include the reactions :

$$(7) \qquad P(OR)_3 + PCl_3 \longrightarrow PCl(OR)_2 + PCl_2{\cdot}OR$$

$$(8) \qquad PCl_3 + PCl(OR)_2 \longrightarrow 2PCl_2{\cdot}OR$$

These are slow compared with reactions (1)—(3), of which they are not the reverse.

In the systems described, any reaction between alcohol and hydrogen chloride is likely to be too slow to make an observable contribution to the formation of alkyl chloride. This cannot be stated of alcohols such as *tert.*-butyl alcohol : the hydrogen chloride formed at the beginning of the mixing can react with the alcohol and form water, which, in turn, by

reaction with the trichloride or chloro-esters, can form hydrogen chloride for further attack on the alcohol. This possibility must be kept in mind in considering the behaviour of such alcohols as *tert.*-butyl alcohol in inorganic non-metallic halide systems. In none of these systems have the esters containing the non-metal been isolated by direct interaction of the halide and the alcohol.

All attempts failed to prepare *tert.*-butyl esters containing phosphorus by the interaction of the trichloride and the alcohol; the products isolated were the alkyl chloride and phosphorous acid. The titration procedure was adapted to cope with the more easily hydrolysed *tert.*-butyl chloride, chlorine other than in this compound being precipitated and separated as pyridine hydrochloride. Table 5 shows the yield of alkyl chloride during 1 hour at 0° when the alcohol (1 mol.) was allowed to react with the trichloride (0·33 mol.) in ethereal solutions of different concentrations. At low concentrations a minimum yield of 25% was obtained, and this was not increased by extending the reaction time to 96 hours. In pentane (Table 6) there was no asymptotic approach to a certain minimum at low concentration, and furthermore, for, *e.g.*, 0·25M-solution the yield increased from 36·1% (1 hour) to 77·4% (10 hours). These data are consistent with the rapid formation of the esters and their ready dealkylation by hydrogen chloride, the effect when ether was solvent probably being due to retention of hydrogen chloride as the ether oxonium salt. This view is in accordance with the rapid and complete dealkylation of di-*tert.*-butyl hydrogen phosphite by hydrogen chloride alone, and with the very much slower dealkylation in dilute ethereal solutions.

The general procedure for preparing trialkyl phosphites, *viz.*, addition of the trichloride (1 mol.) to a solution of the alcohol (3 mol.) and tertiary base (3 mol.) in a solvent such as ether or pentane, was not effective with *tert.*-butyl alcohol; for although 93% of the chlorine was rapidly precipitated as salt, even at −78°, it was the hydrogen phosphite and not the tri-ester which was isolated.

Ethyl glycollate, β-hydroxypropionate, and malate were examined to reveal any special influence of the carbethoxy-group. Reaction sequences conform clearly with those for *n*-butyl alcohol and for octan-2-ol. Comparison of rotatory powers leads to the postulation that the final attachment of chlorine entails inversion of configuration without material loss in rotatory power.

Experimental

All materials were rigorously purified just before use, and solvents were dried.

Butyl Phosphorodichloridite and *Dibutyl Phosphorochloridite*.—Alcohol (1 mol.) was added to phosphorus trichloride (1 mol.) (Gerrard, *loc. cit.*). *n*-Butyl alcohol (74 g.) gave the dichloridite (70%), b. p. 47°/10 mm., d_4^{20} 1·166 (Found: Cl, 40·2; P, 17·55. Calc. for $C_4H_9OCl_2P$: Cl, 40·5; P, 17·7%), and a residue (52·1 g.). *iso*Butyl alcohol (50·0 g.) gave the dichloridite (67·5%), b. p. 42·5°/12 mm., d_4^{22} 1·169, n_D^{20} 1·4642 (Found: Cl, 40·3%), and a residue (17·1 g.). *sec.*-Butyl alcohol (40·0 g.) gave the *dichloridite* (46%), b. p. 61—64°/22 mm., d_4^{20} 1·173, n_D^{23} 1·4655 (Found: Cl, 40·0%), and a residue (11·4 g.). It was not possible to obtain good yields of chloridite by careful addition of alcohol (1 mol.) to the corresponding dichloridite. *n*-Butyl alcohol (12·8 g.) was added dropwise to *n*-butyl phosphorodichloridite (35·0 g.) at −10°; a liquid (6·94 g.), b. p. up to 60°/12 mm., dichloridite (8·57 g.), b. p. 65—70°/20 mm. (Found: Cl, 40·8%), a mixture of chloridite and dibutyl hydrogen phosphite (3·83 g.), b. p. 114—119°/20 mm. (Found: Cl, 11·0%), the hydrogen phosphite (mainly) (9·54 g.), b. p. 122—125°/14 mm. (Found: Cl, 0·75%), and a residue (4·53 g.) were obtained.

A mixture of *n*-butyl alcohol (42·2 g., 1 mol.) and pyridine (1 mol.) in ether (100 c.c.) was added dropwise to the dichloridite (99·8 g., 1 mol.) in ether (100 c.c.) at −10°. Base hydrochloride (100%) and a filtrate, which gave a liquid (10 g.), b. p. 80—100°/13 mm., crude chloridite (80·1 g., 65·9%), b. p. 100—102°/13 mm., a liquid (18·7 g.), b. p. 102—112°/13 mm., and a residue (12·5 g.), were obtained. From the crude material the chloridite (60·5%), b. p. 100—103°/12—14 mm., 55—58°/0·05 mm., d_4^{16} 1·009, n_D^{20} 1·4455 (Found: Cl, 16·45; P, 14·55. Calc. for $C_8H_{18}O_2ClP$: Cl, 16·7; P, 14·6%), was obtained.

Addition of *iso*butyl alcohol (3·38 g., 1 mol.) to the dichloridite (8·0 g., 1 mol.) at −10°, in a stream of carbon dioxide, afforded the dichloridite (1·72 g.), b. p. 47—49°/10 mm., *diiso*butyl *phosphorochloridite* (3·8 g., 40%), b. p. 83—85°/9 mm. (Found: Cl, 16·45. $C_8H_{18}O_2PCl$ requires

Cl, 16·7%), and the hydrogen phosphite (2·4 g.), b. p. 100—106°/14 mm. In the presence of pyridine (1 mol.) in pentane (300 c.c.), the alcohol (25·4 g., 1 mol.) and dichloridite (60 g., 1 mol.) at −10° immediately gave the base hydrochloride (100%), the chloridite (42·1 g., 56%), b. p. 102—105°/20 mm., d_4^{19} 1·007, n_D^{20} 1·4405 (Found: C, 45·8; H, 8·5; Cl, 16·3. Calc.: C, 45·2; H, 8·5; Cl, 16·7%), and a mixture (17·4 g.) of chloridite and phosphite, b. p. 106—117°/19 mm. Addition of the alcohol (2 mol.) and base (2 mol.) to the trichloride (1 mol.) in ether gave the same materials; but distillation was troublesome. Addition of the alcohol (7·4 g., 1 mol.) and base (1 mol.) to the trichloride (1 mol.) in ether afforded base hydrochloride (99·5%), the dichloridite (6·0 g., 40%), b. p. 40—42°/9 mm. (Found: Cl, 39·2%), and chloridite (4·0 g.), b. p. 80—85°/9 mm. (Found: Cl, 17·1%).

From alcohol (8·5 g., 1 mol), pyridine (1 mol.), and the dichloridite (1 mol.) in pentane (200 c.c.) at −10°, *di*-sec.-*butyl phosphorochloridite* (12·0 g., 50%), b. p. 102—104°/23 mm., d_4^{20} 1·024, n_D^{22} 1·475 (Found: Cl, 16·4; P, 14·8%), was obtained.

Dealkylation of Dichloridites and Chloridites by Hydrogen Chloride.—The dry gas was passed into the ester, a U-tube at −80° being attached to the apparatus to retain alkyl chloride. The reaction vessel and U-tube were weighed after different intervals of time. At 25° the dichloridites reacted only slowly. After 14 hr. (dichloridite, 10 g.) there was only a slight wetting of the tube, and the dichloridite was distilled almost unchanged in amount. With *n*-butyl phosphorodichloridite (14·13 g.) after 11 hr. at 65° the decrease in weight of the reaction system was 1·36 g., and the increase in weight of the U-tube was 1·52 g. From the condensate, *n*-butyl chloride (1·0 g.), b. p. 78·5°, n_D^{20} 1·4005, was obtained.

Hydrogen chloride was passed into di-*n*-butyl phosphorochloridite (22·0 g.) at 65° for 48 hr. The reaction vessel first gained and then continuously lost weight, and the residue (7·97 g.) after being kept at 15 mm. weighed 7·87 g. (Found: Cl, nil; P, 38·2. Calc. for HO_2P: P, 48·4%. Calc. for H_3O_3P: P, 37·8%). The U-tube condensate gave *n*-butyl chloride (17·65 g. Calc. for 2RCl: 19·2 g.), b. p. 78·5° (Found: Cl, 37·8. Calc. for C_4H_9Cl: Cl, 38·4%). Similarly, di*iso*butyl phosphorochloridite (25·4 g.) gave *iso*butyl chloride (4·0 g.), b. p. 68·5°, after 6 hr. at 65°, whereas the chloridite (19·0 g.) gave the chloride (2·1 g.), b. p. 68·5°, after 27 hr. at 17°.

Sealed-tube Technique.—Pipettes made to effect quick delivery of definite molar ratios of reagents on a semimicro-scale were calibrated to deliver amounts of the order of 0·250 g. The phosphorus compound was run into a previously constricted tube, solvent, when used, was added (to give a 5% solution of alcohol in solvent, w/w), and alcohol was added to the contents at −78° before sealing. The tubes were opened under dilute aqueous ammonia inside a large flask in such a way as to avoid loss of hydrogen chloride. Chloride ion was then determined by Volhard's method. The loss in readily hydrolysable chlorine is expressed as the % formation of alkyl chloride, the chloro-esters giving chloride ion quickly with water. Results are recorded in Tables 1, 2, and 3. The time intervals were 24 and 72 hr.

TABLE 1. (18°)

Mol. ratio, *n*-BuOH : PCl_3	Yield of RCl (%, based on R·OH) in 24 hr.				Yield of RCl (%, based on R·OH) in 72 hr.			
	No solvent	C_5H_{12}	C_6H_6	Et_2O	No solvent	C_5H_{12}	C_6H_6	Et_2O
3 : 1	44·7	32·4	28·3	26·3	52·3	31·9	33·9	29·7
3 : 2	34·5	25·7	27·5	18·2	35·8	28·4	28·1	23·0
3 : 3	21·6	21·0	21·8	8·0	22·8	23·4	22·8	6·6

TABLE 2. (18°)

Mol. ratio, Bu^nOH : PCl_2·OBu^n	Yield of RCl (%, based on Cl) in 24 hr.				Yield of RCl (%, based on Cl) in 72 hr.			
	No solvent	C_5H_{12}	C_6H_6	Et_2O	No solvent	C_5H_{12}	C_6H_6	Et_2O
6 : 1	48·5	44·8	44·5	42·6	52·8	45·6	44·5	43·5
3 : 1	51·1	47·8	47·8	43·7	55·3	48·9	46·7	43·5
3 : 2	49·3	35·2	36·6	29·2	52·9	36·2	38·0	31·1
3 : 3	31·0	20·4	25·0	19·4	35·4	21·8	25·0	19·5
Bu^tOH : PCl_2·OBu								
6 : 1	42·8	38·6	36·7	33·5	44·0	40·3	32·7	34·8
3 : 1	42·0	45·1	41·5	39·4	42·6	40·3	42·4	38·7
3 : 2	36·0	27·9	30·5	21·9	36·9	31·0	31·8	21·5
3 : 3	18·7	20·5	20·2	9·5	18·8	20·5	21·8	10·4

TABLE 3. (18°)

Mol. ratios $Bu^nOH : PCl(OBu^n)_2$	Yield of RCl (%, based on Cl) in 24 hr. No solvent	C_5H_{12}	C_6H_6	Et_2O	Yield of RCl (%, based on Cl) in 72 hr. No solvent	C_5H_{12}	C_6H_6	Et_2O
6 : 1	84·5	79·0	79·9	74·4	87·2	82·6	75·3	76·3
3 : 1	87·7	79·9	—	72·6	91·3	84·5	79·0	76·3
3 : 2	89·0	82·2	88·1	81·8	91·1	87·2	89·5	81·8
3 : 3	90·5	85·4	89·3	83·4	92·4	89·6	91·8	83·8
$Bu^iOH : PCl(OBu^i)_2$								
6 : 1	78·0	—	56·2	50·1	82·0	—	69·0	54·1
3 : 1	78·0	—	74·2	49·1	77·0	—	79·0	56·1
3 : 2	84·0	—	81·7	68·3	85·5	—	84·0	70·5
3 : 3	86·3	—	85·5	74·5	84·4	—	85·7	76·4
3 : 6	99·8 *	—	95·4	82·1	—	—	—	—

* Based on R·OH.

In another series, vessels fitted with taps were used, and the contents were analysed at shorter time intervals. Weights of dichloridite were of the order 0·500 g., and of the chloridite, 1·000 g. Data are recorded in Table 4.

TABLE 4. (25°)

Mol. ratio $Bu^nOH : PCl_2 \cdot OBu^n$	No solvent RCl, %	Time, min.	C_6H_6 RCl, %	Time, min.	Et_2O RCl, %	Time, min.
1 : 1	19·0	15	18·2	15	13	15
2 : 1	49·8	30	44·7	20	34·2	30
	—	—	49·2	30	42·0	60
$Bu^nOH : PCl(OBu^n)_2$						
1 : 1	89·8	1	63·2	1	35·4	5
	90·5	15	82·4	5	53·0	30
	92·0	120	88·0	30	71·8	60
2 : 1	89·8	1	63·7	1	34·8	5
	91·5	2	77·3	10	48·9	30
	93·4	180	89·1	30	57·8	60

As a check on the titration method, *n*-butyl alcohol (3·7 g., 1 mol.) was added to the chloridite (10·6 g., 1 mol.) at −10°. Volatile matter was removed immediately at −10°; *n*-butyl chloride (3·54 g., 78%), b. p. 77·4° (Found: Cl, 37·9%), and dibutyl hydrogen phosphite (9·0 g., 92%), b. p. 120—125°/10 mm. (Found: P, 15·7%), were obtained. Similarly, the dichloridite (4·37 g., 0·5 mol.) and the alcohol (3·7 g., 1 mol.) at −10° gave alkyl chloride (1·56 g., 42%, based on Cl), b. p. 77·5° (Found: Cl, 37·8%), and hydrogen phosphite (4·5 g., 90%), b. p. 120—125°/10 mm. When only 1 mol. of alcohol to 1 mol. of dichloridite was used, the yield of alkyl chloride was 24%, based on the chlorine.

Reactions with tert.-*Butyl Alcohol.*—The alcohol (3·7 g., 1 mol.) was added (molten, dropwise) to the trichloride (13·74 g., 2 mol.) at −10°. After 1 hr. volatile matter was removed at 20°/20 mm., and the nature of the residue (1·863 g.) (Found: Cl, 0·7; P, 37·7. Calc. for H_3PO_3: P, 37·8%) showed the absence of esters containing phosphorus. The volatile matter had b. p. 51—75°. Similar results were obtained with the reagents 1 mol.: 1 mol., and after the addition of water, *tert.*-butyl chloride (57%), b. p. 52—53° (Found: Cl, 37·8. Calc. for C_4H_9Cl: Cl, 38·4%), was obtained. The ratio being 3 mol. (12·9 g.) of alcohol to 1 mol. of trichloride (7·8 g.), *tert.*-butyl chloride (14·2 g., 88%), b. p. 51° (Found: Cl, 37·9%), and phosphorous acid (Found: P, 37·0%) were immediately obtained. To decrease the rate of reactions solvents were used, and the amount of alkyl chloride formed was estimated by separating the remaining chlorine as pyridine salt. Standard solutions of alcohol and trichloride were mixed at −10° in a specially designed apparatus fitted with a dropping-funnel and a sintered-glass disc, moisture being excluded. After the stated time at 0°, pyridine was added at −10°, and the chlorine content of the precipitate determined. The yield of alkyl chloride was computed by difference. In no case did the filtered solution give a precipitate with ethanol, so conditions were always satisfactory.

Table 5 shows results for a series in which the ratio was 3ROH : PCl_3, the reactants being mixed in ethereal solution so as to give an initial concentration of alcohol as stated. After the reaction mixture had been at 0° for 1 hr., pyridine was added as described. The yield of 25% persisted in more dilute solutions, and for times up to 96 hr. Corresponding results for pentane

are given in Table 6. For, *e.g.*, 0·25M-solution, the yield of 36·1% did not persist with time, but increased to 49·2% (2 hr.), 65·8% (6 hr.), and 77·4% (10 hr.).

TABLE 5. (Ether)

Initial concn. of ROH, g.-mol./l. ...	7·14	6·25	5·0	4·5	4·0	3·5	2·5	0·25
Yield of Bu^tCl, %	86·5	77·6	64·5	51·4	46·2	40·1	25·0	25·0

TABLE 6. (Pentane)

Initial concn. of ROH, g.-mol./l.	7·14	6·25	5·0	4·16	3·57	1·0	0·5	0·25
Yield of Bu^tCl, %	91·4	89·2	87·2	85·0	83·0	75·6	65·3	56·3	36·1

Despite the utmost efforts, tri-*tert.*-butyl phosphite could not be isolated. Phosphorus trichloride (9·16 g., 0·33 mol.) in ether was added to the alcohol (14·8 g., 1 mol.) and pyridine (15·8 g., 1 mol.) in ether at −10°. From the filtrate *di*-tert.-*butyl hydrogen phosphite* (10·0 g., 53·6%), b. p. 48—50°/0·4 mm. (oil-bath never over 65°, otherwise vigorous decomposition) (Found: P, 16·1. $C_8H_{19}O_3P$ requires P, 16·0%), was obtained. Although at −78°, 93% of the chlorine was precipitated as salt, the only ester obtained was the hydrogen phosphite (11·5 g., from ROH, 14·8 g.), b. p. 45°/0·1 mm. (Found: P, 15·9%), the residue weighing 0·40 g.

Hydrogen chloride was passed into the hydrogen phosphite (4·73 g.) at 0°. Volatile matter equivalent to 2·7 g. of alkyl chloride was carried away in 30 min. *tert.*-Butyl chloride actually distilled (1·48 g.) had b. p. 50—51° (Found: Cl, 36·6%), and there was a residue (2·11 g. Calc. for H_3PO_3: 2·00 g.) (Found: P, 37·8%).

By the pyridine-titration method it was shown that the hydrogen phosphite gave only a 4% formation of alkyl chloride after 41 hr. at 25° when the reagent was an ethereal solution of hydrogen chloride (0·1 molar), whereas for a 2M-solution at 0° the yield was 14% after 1 hr.

Reactions with Hydroxy-esters.

The Phosphites.—These were prepared by addition of phosphorus trichloride (1 mol.) to pyridine (3 mol.) and hydroxy-ester (3 mol.) in ether at −10° (Gerrard, *loc. cit.*). Precipitation of base hydrochloride was rapid, even at −78°. *Triscarbethoxymethyl phosphite* (81% yield) had b. p. 125—126°/0·03 mm., n_D^{20} 1·4508, d_4^{20} 1·214 (Found: C, 41·8; H, 6·1; P, 9·3. $C_{12}H_{21}O_9P$ requires C, 42·4; H, 6·2; P, 9·1%). *Tris*-2-*carbethoxyethyl phosphite* (78%) had b. p. 143—144°/0·02 mm., n_D^{20} 1·4506, d_4^{20} 1·151 (Found: C, 46·7; H, 6·8; P, 8·5. $C_{15}H_{27}O_9P$ requires C, 47·1; H, 7·1; P, 8·1%). *Tris*-1 : 2-*dicarbethoxyethyl phosphite* (from ethylmalate) could not be distilled in pure condition owing to decomposition to ethyl fumarate, b. p. 97—98°/13 mm., n_D^{20} 1·4411, and hydrogen phosphite. The best distilled specimen had b. p. 170—180°/0·01 mm., $[\alpha]_D^{20}$ −60·17° (from R·OH, $[\alpha]_D^{21}$ −10·55°), d_4^{20} 1·199 (Found: C, 47·2; H, 6·3; P, 6·05. $C_{24}H_{39}O_{15}P$ requires C, 48·2; H, 6·6; P, 5·2%).

The Hydrogen Phosphites.—Trichloride (1 mol.) was added dropwise to the hydroxy-ester (3 mol.) at −10°, in a stream of nitrogen. At 18°/12 mm. (0·5 hr.) and then at 0·2 mm. (2 hr.), the temperature being gradually raised to 50°, volatile matter was removed and collected in a trap at −78°. From the residue *biscarbethoxymethyl hydrogen phosphite* (11·3 g.), b. p. 112°/0·03 mm., n_D^{20} 1·4430, d_4^{20} 1·255 (Found: C, 38·4; H, 6·0. $C_8H_{15}O_7P$ requires C, 37·8; H, 6·0%), and from the condensate ethyl chloroacetate (4·75 g.), b. p. 44—45°/14 mm., n_D^{20} 1·4213, were obtained from the glycollate (15·6 g.).

Similarly, ethyl β-hydroxypropionate (17·7 g.) afforded ethyl β-chloropropionate (5·55 g.), b. p. 64·5°/20 mm. (Found: Cl, 26·0. Calc. for $C_5H_9O_2Cl$: Cl, 26·0%), and *bis*-2-*carbethoxyethyl hydrogen phosphite* (12·5 g.), b. p. 132—133°/0·05 mm., n_D^{20} 1·4456, d_4^{20} 1·192 (Found: C, 42·7; H, 7·0. $C_{10}H_{19}O_7P$ requires C, 42·6; H, 6·8%). By the same procedure of isolation, the chloroacetate (1·7 g.) (Found: Cl, 29·0. Calc. for $C_4H_7O_2Cl$: Cl, 28·9%) and the hydrogen phosphite (3·8 g.) (Found: P, 12·3. Calc. for $C_8H_{15}O_7P$: P, 12·2%) were obtained after hydrogen chloride had been passed into the phosphite (5·8 g.) for 3·5 hr. at −10°. The phosphite (6·5 g.) and hydrogen chloride (2 hr. at −10°) gave the β-chloropropionate (2·1 g.) and the hydrogen phosphite (4·55 g.) (Found: P, 11·1. Calc. for $C_{10}H_{19}O_7P$: P, 11·0%).

Into the undistilled phosphite of ethyl malate (8·6 g., α_D^{23} − 86·12°, l = 1) and ether (2 c.c.), hydrogen chloride was passed for 8 hr. at −10°. Volatile matter was removed as before, and ethyl chlorosuccinate (2·0 g.), b. p. 59—60°/0·1 mm., $[\alpha]_D^{25}$ +32·41° (Found: Cl, 16·8. Calc. for $C_6H_{13}O_4Cl$: Cl, 17·0%), and a residue (6·8 g. Calc.: 6·6 g.) (Found: P, 7·0. Calc. for $C_{16}H_{27}O_{11}P$: P, 7·3%), were obtained.

Addition of Hydroxy-ester to Phosphorus Trichloride.—Ethyl glycollate (15·6 g., 1 mol.) was added dropwise to the trichloride (2 mol.) at −10° in a stream of nitrogen. Volatile matter being removed at 20°/12 mm., *carbethoxymethyl phosphorodichloridite* (19·1 g.), b. p. 91—92°/13 mm., n_D^{20} 1·4750, d_4^{20} 1·347 (Found: Cl, 34·3; P, 15·2. $C_4H_7O_3Cl_2P$ requires Cl, 34·6; P, 15·1%), *biscarbethoxymethyl phosphorochloridite* (3·5 g.), b. p. 117°/0·2 mm., n_D^{20} 1·4615, d_4^{20} 1·262 (Found: Cl, 13·0; P, 11·7. $C_8H_{14}O_6ClP$ requires Cl, 13·0; P, 11·4%), and residue (2·3 g.) (undistilled at 180°/0·05 mm.) were obtained.

Similarly, ethyl β-hydroxypropionate (17·7 g.) gave *2-carbethoxyethyl phosphorodichloridite* (22·05 g.), b. p. 58—59°/0·2 mm., n_D^{20} 1·4740, d_4^{20} 1·294 (Found: Cl, 32·4; P, 14·3. $C_5H_9O_3Cl_2P$ requires Cl, 32·4; P, 14·2%), a fraction (3·45 g., mainly hydrogen phosphite), b. p. 132—133°/0·1 mm. (Found: Cl, 1·9%), and a residue (2·1 g.).

Ethyl malate ($[\alpha]_D^{20}$ + 10·45°, 24·6 g.) gave 1 : 2-*dicarbethoxyethyl phosphorodichloridite* (22·6 g.), b. p. 92—93°/0·2 mm., $[\alpha]_D^{20}$ +84·61°, n_D^{20} 1·4719, d_4^{20} 1·286 (Found: Cl, 24·3; P, 10·7. $C_8H_{13}O_5Cl_2P$ requires Cl, 24·4; P, 10·6%), and a residue (9·9 g.) which decomposed at 160°.

Other Reactions.—In the proportion required for the reaction $2P(OR)_3 + PCl_3 = 3PCl(OR)_2$, the trichloride (2·34 g., 1 mol.) and triscarbethoxymethyl phosphite (11·55 g., 2 mol.) were heated at 90—100° for 2·5 hr. The dichloridite (1·9 g.), b. p. 72—73°/3 mm., the chloridite (7·2 g.), b. p. 112—113°/0·15 mm. (Found: Cl, 12·7. Calc. for $C_8H_{14}O_6ClP$: Cl, 13·0%), the phosphite (1·6 g.), b. p. 146°/0·15 mm., n_D^{20} 1·4511, and a residue (2·4 g.) which decomposed at 205° were obtained. With the reagents in the proportion trichloride (2 mol.) and phosphite (18·7 g., 1 mol.), the mixture being at 55—60° for 3 hr., the dichloridite (10·65 g.), b. p. 73—74°/3 mm. (Found: Cl, 34·4%), the chloridite (9·65 g.), b. p. 101—103°/0·07 mm. (Found: Cl, 13·0%), unchanged phosphite (1·4 g.), b. p. 141°/0·1 mm., and a residue (2·05 g.) were obtained. The dichloridite (3·76 g., 1 mol.) and the phosphite (6·25 g., 1 mol.) were heated at 90—100° for 3 hr.; the dichloridite (1·8 g.), the chloridite (4·35 g.), b. p. 102—103°/0·07 mm., and a third fraction (2·7 g.), b. p. 114—122°/0·05 mm., were obtained.

Tris-2-carbethoxyethyl phosphite (14·4 g., 2 mol.) and trichloride (2·6 g., 1 mol.) after being at 70° for 3 hr. gave the phosphorodichloridite (3·5 g.), b. p. 58—59°/0·2 mm., the *phosphorochloridite* (3·75 g.), b. p. 107—108°/0·04 mm., n_D^{20} 1·4601, d_4^{20} 1·198 (Found: Cl, 11·7; P, 10·7. $C_{10}H_{18}O_6ClP$ requires Cl, 11·8; P, 10·3%), a third fraction (1·15 g.), b. p. 114—137°/0·07 mm., a mixture of phosphite and hydrogen phosphite (2·45 g.), b. p. 138—145°/0·1 mm., n_D^{20} 1·4472, and a residue (4 g.) which decomposed at 205°. Reaction between the phosphite and dichloridite occurred; but apart from recovery (50%) of the latter, material of a wide distillation range was obtained.

Crude tris-1 : 2-dicarbethoxyethyl phosphite (α_D^{23} −86·12°, l = 1) (9·3 g., 1 mol.) and trichloride (2 mol.), after being at 55—60° for 3·5 hr., gave the dichloridite (4·1 g.), b. p. 92—93°/0·2 mm., $[\alpha]_D^{20}$ − 82·81° (Found: Cl, 24·0%), and a residue (6·4 g.) (Found: Cl, 5·9%).

To prepare the chloridite, a mixture of ethyl glycollate (3·47 g., 1 mol.) and pyridine (1 mol.) in ether (20 c.c.) was added dropwise with vigorous shaking to the dichloridite (6·83 g., 1 mol.) in ether (20 c.c.) at −10°. The base hydrochloride (100%) was precipitated, and from the filtrate dichloridite (0·95 g.), chloridite (5·05 g., 55%) (Found: Cl, 12·7%), the phosphite (1·5 g.), b. p. 143°/0·1 mm., n_D^{20} 1·4510, and a residue (1·2 g.) were obtained. The chloridite (8·88 g., 1 mol.) with ethyl glycollate (1 mol.) and pyridine (1 mol.) in ether gave immediately at −10° the base hydrochloride (100%) and the phosphite (90%), b. p. 125—126°/0·03 mm., n_D^{20} 1·4512.

Similarly, ethyl β-hydroxypropionate (6·35 g., 1 mol.), pyridine (1 mol.), and the dichloridite (1 mol.) gave base hydrochloride (98%), dichloridite (2·75 g.), the chloridite (3·95 g.), b. p. 103—104°/0·03 mm (Found: Cl, 11·8%), a mixture of phosphite and hydrogen phosphite (2·8 g.), b. p. 137—149°/0·05 mm., and a residue (2·1 g.).

Similarly, ethyl malate (7·1 g., 1 mol.), base (1 mol.), and dichloridite (1 mol.) gave hydrochloride (100%), the dichloridite (2·7 g.), b. p. 72—74°/0·05 mm., and a residue (12·15 g.) which decomposed at 160°, but which with ethyl malate (2·49 g.) and base (1·04 g.) gave the hydrochloride (98%) and a mixture (12·6 g.) of phosphite and hydrogen phosphite, b. p. 170—180°/0·01 mm.

Messrs. C. Baggallay and B. K. Howe carried out exploratory and check experiments.

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395. *Studies of N-Halogeno-compounds. Part IV.* The Reaction between Ammonia and Chlorine in Aqueous Solution, and the Hydrolysis Constants of Chloroamines.*

By R. E. Corbett, W. S. Metcalf, and F. G. Soper.

The reaction between ammonia and chlorine or hypochlorous acid in dilute aqueous solution has been examined spectrophotometrically. The product in solutions of pH < 3 is nitrogen trichloride, of pH 3—5 dichloroamine, and of pH > 8 monochloroamine. In strongly alkaline solution, chloroamine is hydrolysed to hypochlorite ions.

The reaction between chlorine and ammonia in aqueous solution has been examined by a distribution method by Chapin (*J. Amer. Chem. Soc.*, 1929, **51**, 2113); above pH 4·4 dichloroamine was formed and below pH 4·4 nitrogen trichloride, the change in product occurring sharply at this pH. Above pH 8·5 only monochloroamine was obtained. Chapin also identified the dichloroamine by analysis. The results of the spectroscopic examination of solutions much more dilute than those used by Chapin are in substantial agreement with these conclusions. Above pH 8, the absorption spectra show a mixture of chloroamine and hypochlorite, from 5 to 8 a mixture of mono- and di-chloroamine, and below pH 3 only nitrogen trichloride.

The absorption spectra of these unstable solutions were measured by the flow method described in a previous paper (Metcalf, *J.*, 1942, 148). In the Figure are plotted the ultra-violet absorption spectra of hypochlorite ions and chloroamine. Those of dichloroamine and nitrogen trichloride have been published previously (*loc. cit.*). At any one pH only two absorbing substances are present, so that the points of intersection of the curves are isosbestic points (cf. Flexser, Hammett, and Dingwall, *J. Amer. Chem. Soc.*, 1935, **57**, 2103), and the curves for equilibrium mixtures pass through them. As the total concentration of hypochlorous acid liberated on hydrolysis is known, the proportion of it present as hypochlorite, chloroamine, dichloroamine, or nitrogen trichloride can be calculated from the extinction curve of the equilibrium mixture.

Whilst the equilibrium between chloroamine and hypochlorite is immediately attained and the solutions are relatively stable, the equilibria between chloroamine and dichloroamine, and between dichloroamine and nitrogen trichloride are approached but slowly. Moreover, solutions that contain dichloroamine are very unstable (Table 2) and cannot be left for any length of time to attain equilibrium. It has therefore only been possible to determine the equilibrium constant of the first of the following reactions:

$$NH_2Cl + OH^- \rightleftarrows NH_3 + OCl^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$H^+ + 2NH_2Cl \rightleftarrows NHCl_2 + NH_4^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

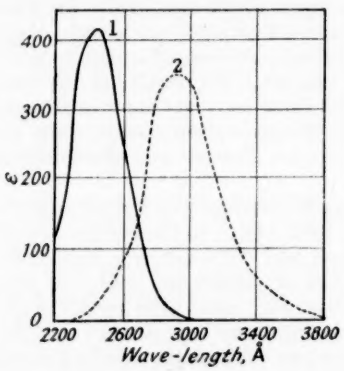
$$H^+ + 3NHCl_2 \rightleftarrows 2NCl_3 + NH_4^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The Hypochlorite–Chloroamine Equilibrium.—The equilibrium $4H^+ + 3Cl^- + NCl_3 \rightleftarrows NH_4^+ + 3Cl_2$, which might perhaps be expected in sufficiently acid solutions, could not be detected in concentrated hydrochloric acid. In the equilibrium, $NH_2Cl + OH^- \rightleftarrows NH_3 + OCl^-$, the total active chlorine is estimated by iodometric titration and the amount of it present as hypochlorite and chloroamine is deduced from the extinction at 3100 Å (see Figure). The hydroxyl-ion concentration is taken as the concentration of the sodium hydroxide present. The total ammonia added is known, and the concentration of ammonia in the solution is obtained by subtracting the concentration of chloroamine from it. Thus all the concentration terms (in moles per litre) in the expression $[NH_3][OCl^-]/[NH_2Cl^-][OH^-] = K'$ are known. The values of K' for various concentrations of sodium hydroxide, ammonia and active chlorine are given in Table 1.

* Previous papers that form a part of this series are those by Mauger and Soper, *J.*, 1946, **71**; Edmond and Soper, *J.*, 1949, 2942; and Hurst and Soper, *J.*, 1949, 107.

The effect of displacing the equilibrium by decreasing the ammonia concentration from 0·01M to 0·002M while keeping the other concentrations constant is shown in Table 1*A*. Table 1*B* shows the effect of increasing the hydroxyl-ion concentration from 0·5M to 2·5M, and Table 1*C* illustrates the effect of varying the concentration of ammonia. In the last series the possible percentage error is greater than in 1*A* or 1*B*; since, of the various equilibrium concentrations that of the hypochlorite ion is measured directly with an estimated error of ±2%. This introduces similar errors in the deduced concentrations of NH_2Cl(= [total active Cl] − [OCl^-]) and of NH_3(= [total NH_3] − [NH_2Cl]) except in series *C* where the difference (total [NH_3] − [NH_2Cl]) is smaller and the percentage error larger. The overall mean value of K' is $1·6 \times 10^{-3}$.

K' is related to the hydrolysis constant k_h of the hydrolysis of monochloroamine, $NH_2Cl + H_2O \rightleftarrows NH_3 + HOCl$, by the equation $K_h = K'K_w/K_a$, where K_w is the ionic product for water and K_a is the acid ionisation constant of hypochlorous acid.



1. *Chloroamine.*
2. *Hypochlorite ion.*

If the activity coefficient of neutral molecules is unity and those of univalent ions are equal at a given ionic strength, then K' and K_h are approximately independent of ionic strength and unchanged by the substitution of activities for concentrations.

TABLE 1.

[NaOH], M	[Total NH_3], M	Active Cl, as [HOCl], 10^{-3}M	Active Cl, as OCl′, %	$10^3K'$ (15°)	[NaOH], M	[Total NH_3], M	Active Cl, as [HOCl], 10^{-3}M	Active Cl, as OCl′, %	$10^3K'$ (15°)
				A					
0·5	0·010	2·72	10·0	1·67	0·5	0·0020	2·20	51·0	1·90
0·5	0·0060	2·48	17·4	1·66	1·0	0·0020	2·46	65·0	2·10
				B					
0·5	0·010	2·43	8·45	1·52	0·7	0·010	3·20	12·9	1·52
2·5	0·010	2·64	31·0	1·55	0·8	0·010	3·06	15·1	1·64
0·5	0·010	3·23	10·0	1·57	0·9	0·010	3·04	15·5	1·51
0·6	0·010	2·31	9·9	1·70					
				C					
0·8	0·010	5·04	18·3	1·63	0·8	0·0060	3·70	22·6	1·23
0·8	0·0090	5·12	17·5	1·27	0·8	0·0050	3·72	32·5	1·62
0·8	0·0080	4·40	23·0	1·77	0·8	0·0040	3·28	42·4	1·95
0·8	0·0070	4·45	25·0	1·47					

The value of K_w being taken as $4·7 \times 10^{-15}$ (" International Critical Tables ") and that of K_a as $2·7 \times 10^{-8}$ (Ingham and Morrison, *J.*, 1933, 1200), the value of the hydrolysis constant K_h is $2·8 \times 10^{-10}$ at 15°.

The Monochloroamine–Dichloroamine Equilibrium.—The rapid decomposition of dichloroamine does not permit a test of the constancy of this equilibrium over a period of time, although changes in the spectra were much slower after 3 hours. The displacement

of the equilibrium with increasing acidity is due to the removal of free ammonia as NH_4^+, equation (2) giving the overall reaction. Absorption curves of the solution with 10^{-3}M-hypochlorous acid and 5×10^{-3}M-ammonia buffered with phosphate showed an instantaneous disappearance of hypochlorite ion and the presence of monochloroamine and dichloroamine over the pH range 5—8. We do not consider estimates of the relative amounts present in this unstable solution satisfactory for the evaluation of the equilibrium constant involving dichloroamine. Below pH 3, with ammonia solution from 5×10^{-3}M to $1{\cdot}5 \times 10^{-1}$M and hypochlorous acid from $2{\cdot}25$ to 4×10^{-3}M, only nitrogen trichloride is present.

Equilibria involving nitrogen trichloride are approached slowly. A solution of hypochlorous acid and ammonia in N/10-hydrochloric or N/10-acetic acid contained one third of the active chlorine as nitrogen trichloride, immediately after being mixed. After 1 hour, two thirds was present as the trichloride, and after 2 and 3 hours no dichloroamine remained. This disappearance of dichloroamine from solutions more acid than pH 3 may be due to the relative instability of dichloroamine.

Table 2 shows that solutions which have been proved spectroscopically to contain dichloroamine are much the most unstable, there being a minimum instability of mixtures of ammonia and hypochlorous acid in the pH range 4—5.

TABLE 2.

pH	2·8	3·0	3·9	4·4	6·3—9·2
Time of half decomp. at 15°	10 hr.	7 hr.	10 min.	20 min.	>3 hr.

Solutions of nitrogen trichloride in water are stabilised by small amounts of acid, and those of chloroamine by small amounts of alkali, such as a slight excess of ammonia. Anhydrous solutions of both nitrogen trichloride and of chloroamine in organic solvents are comparatively stable in the absence of light. These facts suggest that the slow decomposition of both compounds in water may perhaps involve the intermediate formation of the unstable dichloroamine as a first step.

None of the spectra of solutions described in this paper was noticeably affected by addition of M/10-sodium chloride, or by use of chlorine water in place of pure hypochlorous acid.

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396. *Toxic Fluorine Compounds containing the* C–F *link. Part IX.* Preparation of Carbon-labelled Sodium Fluoroacetate on a Micro-scale.*

By B. C. SAUNDERS and T. S. WORTHY.

Pure sodium fluoroacetate labelled with ^{14}C in the methylene group has been prepared on a 100-mg. scale. A description is given of a specially designed micro-autoclave suitable for microfluorination. A convenient ampoule breaker has been devised to meet the special needs of this kind of work. Radioactive sodium fluoroacetate is to be used to test theories of fluoroacetate poisoning.

SINCE 1941 we have carried out extensive work on compounds containing the CH_2F group and possessing pronounced physiological properties (McCombie and Saunders, *Nature*, 1946, **158**, 382; Saunders and Stacey, *J.*, 1948, 1773). Thus, during a ten-minutes exposure to a concentration of *ca.* 0·1 mg. of methyl fluoroacetate per l., small animals exhibited no symptoms, but after 30—60 minutes convulsions occurred, followed by death. Many compounds related to this ester were synthesised and their activity examined. We deduced that for high toxicity the compound must be capable of conversion *in vivo* by

* Part VIII, *J.*, 1949, 2774.

oxidation and/or hydrolysis into fluoroacetic acid (Saunders, *J.*, 1949, 916). We also showed that in the series of ω-fluorocarboxylic acids, $F{\cdot}[CH_2]_n{\cdot}CO_2H$, when *n* is odd the compound is toxic and when *n* is even it is non-toxic (Saunders, *Nature*, 1947, **159**, 491; Buckle, Pattison, and Saunders, *J.*, 1949, **1471**). Further, fixation of the α- and β-carbon atoms of the toxic methyl γ-fluorobutyrate in a ring system resulted in a compound of negligible toxicity (Pattison and Saunders, *J.*, 1949, 2745). The effects of methyl fluoroacetate and of sodium fluoroacetate *in vivo* are similar. Even when the dose is many times the lethal, a latent period precedes the onset of convulsions and subsequent death. Marais (*Onderstepoort J. Vet. Sci. Animal Ind.*, 1944, **20**, 67) isolated potassium fluoroacetate from the S. African plant "Gifblaar," *Dichapetalum Cymosum*, which is a well-known hazard to cattle. Sodium fluoroacetate acts as a systemic and contact insecticide (David, *Nature*, 1950, **165**, 493).

In 1948, Peters reported (*Proc. Roy. Soc. Med.*, 1948, **41**, 781): "There is not yet known any case in which fluoroacetate inhibits a single isolated enzyme." This is in contradistinction to the powerful anti-choline esterase activity of the phosphorofluoridates (fluorophosphonates; cf. McCombie and Saunders, *Nature*, 1946, **157**, 776).

Kalnitsky and Barron (*Arch. Biochem.*, 1949, **3**, 215), using kidney homogenate, found that fluoroacetate and γ-fluorobutyrate inhibited the oxidation of acetate, butyrate, etc., and that, *in vitro*, citrate accumulated in the presence of fluoroacetate. Liébecq and Peters (*J. Physiol.*, 1949, **108**, 215; *Biochim. Biophys. Acta*, 1949, **3**, 215) suggested that fluoroacetate entered the tricarboxylic acid cycle *via* the synthesis of a fluorotricarboxylic acid and by some means "jammed" the oxidation of citrate. Lotspeich, Peters, and Wilson (*J. Physiol.*, 1951, **115**, 25P; *Biochem. J.*, 1952, **51**, 20) also investigated the effect of "inhibitor fractions" isolated from tissues poisoned by fluoroacetate and found that the fluorocarboxylic acid fractions inhibited the reactions of aconitase.

The preparation of labelled sodium fluoroacetate will enable the formation of the fluorotricarboxylic acid to be further investigated. Thus the isolation, from tissues treated with radioactive sodium fluoroacetate, of radioactive material containing fluorine and chromatographically similar to the "tricarboxylic" acids would be strong evidence for the hypothesis that citrate accumulation is due to the formation of a fluorocitrate or related compound. Further the use of the radioactive "fluorotricarboxylic acid" fraction in a system containing aconitase should permit of the isolation of a radioactive enzyme–inhibitor complex.

The starting material for our preparation of radioactive sodium fluoroacetate was $^{14}CH_2Br{\cdot}CO_2H$ obtained from the Radiochemical Centre, Amersham. The acid had a total activity of 1·02 mc in 136 mg., and was supplied in a sealed ampoule. Because of the high cost and deliquescence of the material and the danger of ingestion, it was necessary to design a special ampoule breaker which could easily crack the ampoule in an evacuated system so that the radioactive acid could be transferred quantitatively and collected in a cooled U-tube by continuous pumping to high vacuum.

Bromoacetic acid could not be fluorinated directly. We were able to convert it quantitatively into methyl bromoacetate on a micro-scale. Fluorination of the ester at ordinary pressure gave poor yields and the adaptation of the method to small quantities of radioactive material proved difficult. It was, therefore, decided to use Saunders and Stacey's method (*loc. cit.*) in which fluorination is by potassium fluoride in a rotating autoclave. A micro-autoclave was designed for work with 100-mg. of volatile material. The volatile product contained only methyl bromoacetate and methyl fluoroacetate and the percentage composition was determined by refractive-index measurement and reference to a previously constructed calibration curve. The accuracy of the estimation was confirmed by fluorine analysis of known mixtures and in one instance by the fluorine analysis of the product.

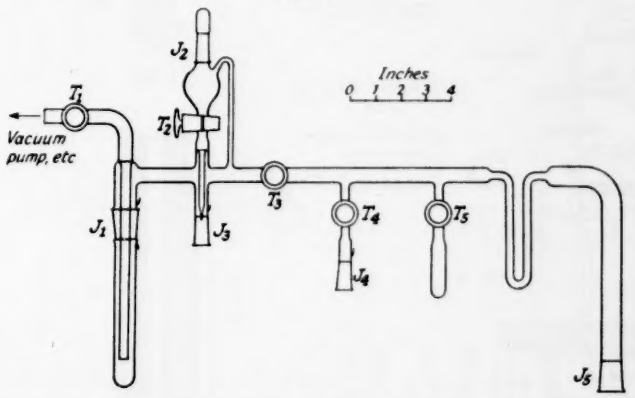
Fractional distillation of the product (*ca.* 50 mg.), by a special condensation unit (Fig. 5), gave methyl fluoroacetate of 94% purity. This was converted into sodium fluoroacetate by titration with sodium hydroxide solution in an apparatus containing a glass electrode and calomel half cell. The pure product was isolated by freeze-drying. Incidentally the value of the titre was a measure of the purity of the product as the equivalent weights of methyl bromoacetate and methyl fluoroacetate are sufficiently different.

Experimental

The vacuum apparatus is shown in Fig. 1. Apiezon " M " grease was used for all taps and joints, except J_1, J_2, J_3, T_2, and T_3 where silicone grease was employed.

Methyl Bromoacetate.—The radioactive bromoacetic acid was contained in a sealed-glass ampoule. In order to open this safely and conveniently a breaker (Fig. 2) was made from gun-metal alloy or stainless steel. The main component B had B24 cones about E and H, and was threaded on its inner surface. The ampoule was placed in HG, and held in place by the threaded cylinder A. The breaking-plug C, which had a rectangular-sectioned projection at its outer end, was screwed into E until its inner end reached F. After greasing, the knurled head D was placed over the end E, the rectangular hole in D fitting over the projection on C. The whole was then attached at J_5, which surrounded H. A tube, containing a small piece of soft iron sealed in glass to serve as a stirrer, was attached at J_3. In those experiments in which we diluted the radioactive bromoacetic acid, a break-seal ampoule containing the required amount of non-radioactive bromoacetic acid was attached at J_4 and a small magnetic breaker was placed next to the tip of the ampoule. After evacuation, T_3 was closed and D rotated slowly, thus propelling the breaking-plug C towards the ampoule. When it reached the ampoule an increased resistance to turning could be felt : when the ampoule broke a definite " kick " could be detected.

Fig. 1.



The U-tube was cooled in liquid oxygen, T_3 opened, and the whole apparatus evacuated continuously until all the radioactive bromoacetic acid had been transferred to the U-tube.

When dilution was necessary, T_3 was closed, the tip of the ampoule containing inactive bromoacetic acid was broken by oscillating a magnet about J_4, and the contents of this ampoule transferred to the U-tube. Dry air was then let into the apparatus *via* T_1 and the U-tube warmed to 55° and then cooled. This process was repeated twice. The mixed acid was transferred under high vacuum to tube J_3, where the process of mixing was repeated, this time with the help of the magnetic stirrer. When dilution was not required, the radioactive acid was transferred directly from the U-tube to J_3. In both cases a small sample of the homogeneous acid was transferred to the tube closed by T_5, and this could later be used for counting.

To the acid (*ca.* 100 mg.), dry ether (1 ml.) was added *via* J_2 and T_2. T_3 was closed and T_1 opened to the atmosphere, with suitable drying tubes. A solution of diazomethane (*ca.* 40 mg.) in ether (3 ml.) was then slowly added to the ice-cold solution of the acid. The two solutions soon formed separate layers which were gently mixed by means of the magnetic stirrer. The tube J_1 was cooled in ice–salt and the tube J_3 warmed to 55°, the ether and excess of diazomethane being collected in J_1. In preliminary experiments it was found essential to use a grease which was not very soluble in ether, otherwise the lubricant was washed down into tube J_3, making complete recovery of the methyl bromoacetate impossible. The tube J_3 was next cooled in liquid oxygen while the ether was removed under reduced pressure *via* T_1. By allowing J_3 to warm to room temperature for a short time, with the water-pump still running, the last traces of ether were removed. The methyl bromoacetate was then transferred to a tube at J_4 and T_4 was closed.

In a typical experiment 135·5 mg. of acid gave 144·3 mg. (97%) of ester, n_D^{15} 1·4582.

Fluorination of Methyl Bromoacetate.—The microautoclave *J* (Fig. 3) was designed so that losses could not occur on introduction or removal of material. Joints were vacuum- and pressure-tight, and volatile material was introduced and removed through a special attachment to the vacuum system. Thorough mixing was achieved by vibration in a vertical plane. The autoclave, made of stainless steel, had a socket (120°) into which fitted a stainless-steel cap *K* whose taper was slightly more acute, so that when the locking-nut *L* was screwed down firmly *K* and *J* came into contact along a circle. The attachment *M* was used for filling the autoclave. Its lower cone was similar to *K*, except for a central hole, which connected with a length of copper tubing and thence with a standard brass cone.

Potassium fluoride (*ca.* 65 mg.) and 12—14 stainless-steel balls (radius 3/32″) were placed in *J*, and *M* was then screwed down tightly, a trace of silicone grease being applied to the joint.

FIG. 2.

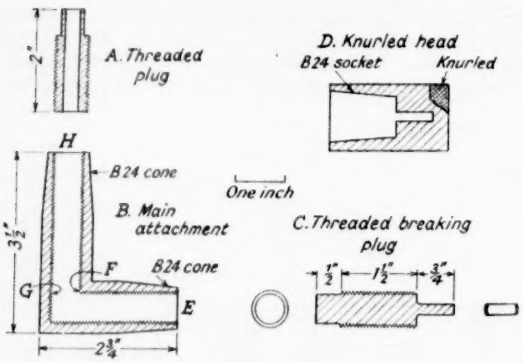


FIG. 3.

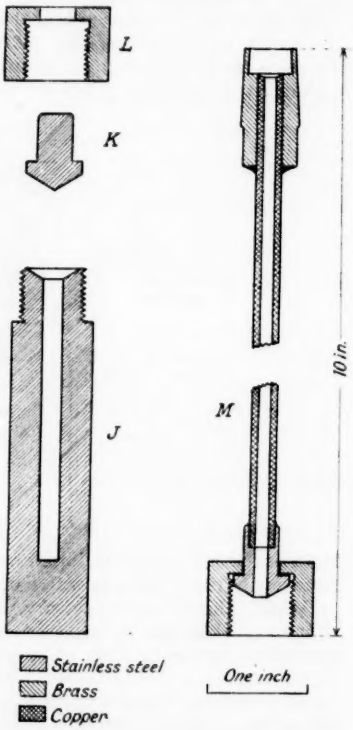
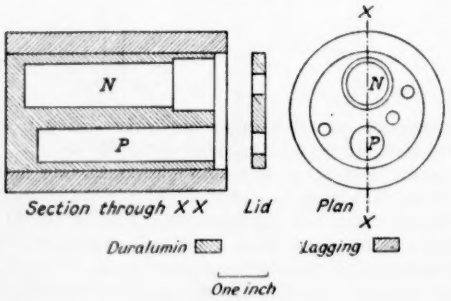


FIG. 4.



The whole was then attached at J_3 and pumped to high vacuum for 2 hr. to remove any water. In transference of methyl bromoacetate to the autoclave, T_1 was closed, T_4 opened, and *J* cooled in liquid oxygen, the copper tube and brass cone being kept at about room temperature. With *J* still cooled, tube J_1 was also cooled in liquid oxygen, while the system was pumped, the tube and cone being warmed to *ca.* 50°. Any methyl bromoacetate which had been retained in the tube was transferred either to *J* or to tube J_1; any ester which might have collected in J_1 was transferred to *J* and the process repeated until no more collected in J_1. Dry air was let in *via* T_1, *M* was detached, and the cap *K* and nut *L* were used to seal the autoclave.

The lagged heating-block (Fig. 4) was made of duralumin. The microautoclave was placed in the hole *N* and a 50-w heater in *P*. The whole was then mechanically shaken in a vertical plane for 3½ hr. at 220°, the axis of the autoclave being vertical. After cooling, *L* and *K* were removed from *J*, and replaced by *M*. This was attached at J_3, and the product transferred to a small tube attached by means of an adaptor at J_4.

Some decomposition of the methyl bromoacetate occurred during the reaction. [After

heating of 158·2 mg. of methyl bromoacetate without potassium fluoride at 220° in the autoclave for 3½ hr., 140·1 mg. (89%) of the ester were recovered unchanged.]

The percentage of fluoroacetate in the product was estimated by comparing the values of the refractive index with those found for known mixtures of methyl bromoacetate and methyl fluoroacetate. Results are tabulated. The yield quoted makes no allowance for the methyl bromoacetate recovered.

Methyl bromoacetate (mg.)	Product mg.	n	$CH_2F{\cdot}CO_2Me$ (%) in product	Yield (%)
102·6	36·7	1·3897	72	43
113·1	63·8	1·4022	56	53
93·0	36·2	1·3965	63	41
123·6	43·0	1·3962	63	37
114·0	65·2	1·4096	47	45

Removal of Residual Methyl Bromoacetate.—The fractionation unit (Fig. 5) was attached by J_6 at J_3, the tube containing the fluorinated ester being attached at J_7. The U-tube S was

FIG. 5.

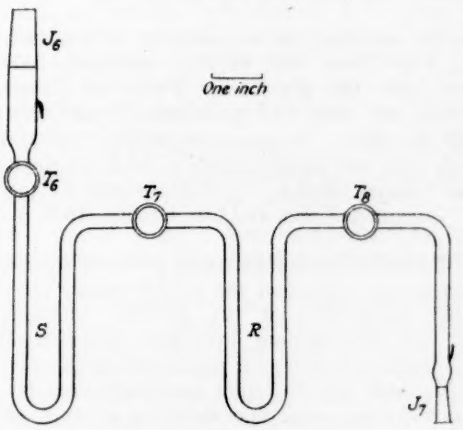
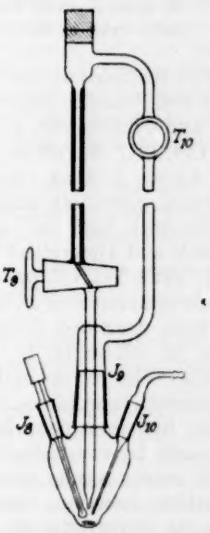


FIG. 6.



cooled in liquid oxygen, R in a bath of melting ethyl malonate (−54°), and the tube at J_7 in a bath of melting carbon tetrachloride (−25°). The system was continuously evacuated, T_6, T_7, and T_8 being open. When all the mixture had been transferred from the tube J_7 to S and R, T_1 and T_7 were closed. The material from S was transferred to a small weighed tube at J_4, while that from R was transferred to the tube J_7.

Preliminary experiments were carried out on the micro-fractionation of synthetic mixtures of non-radioactive methyl bromoacetate and methyl fluoroacetate of known composition. For example, with mixtures containing 47—49% of methyl fluoroacetate, the lower-boiling fraction (collected in S) contained 94—100% of fluoroacetate. Moreover, 77—57% of the fluoroacetate from the original mixture was now in this lower-boiling fraction. When material from the micro-autoclave was used the percentage of fluoroacetate in the lower-boiling fraction was within the range 94—100%, as shown by refractive-index measurement. Furthermore, infra-red spectroscopy proved that this material contained at least 90% of methyl fluoroacetate.

Sodium Fluoroacetate.—The titration cell (Fig. 6, shown attached to a pressure-equalised burette), containing a small iron strip sealed in glass to serve as a stirrer, and with stoppers at J_8 and J_{10}, was attached by J_9 at J_3. The methyl fluoroacetate (42 mg.) was then transferred to this cell under high vacuum. After removal of the cell, water (1 ml.) was immediately added to avoid loss by volatilisation. A glass electrode was placed at J_8 and a tube connected to a calomel half-cell at J_{10}. The cell was attached to the burette, with T_{10} open. The mixture

was stirred magnetically and slowly titrated with N-sodium hydroxide (0·43 ml.) to pH 11 (42 mg. of methyl fluoroacetate requires 0·45 ml. of N-NaOH).

The electrodes and burette were removed and washed. The solution was removed and the pure sodium fluoroacetate (45 mg.) isolated by freeze-drying.

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397. *Hydrazine. Part III.* The Hydrazinium Salts of Complex Fluoro-Acids of Tin, Antimony, and Bismuth.*

By W. PUGH.

(*With Notes on the Optical Properties of the Crystals.* By H. C. G. VINCENT.)

Hydrazinium fluoro-salts of tin, antimony, and bismuth have been made (cf. chlorostannates; Pugh and Stephen, *J.*, 1952, 4138; 1953, 354), but those of arsenic could not be obtained. There is evidence that ketazinium fluoro-salts exist in solution, but it has not been possible to crystallise them.

COMPLEX fluorides of the hydrazinium ion described in the literature include the fluoro-silicate and -titanate (Ebler and Schott, *J. pr. Chem.*, 1910, **81**, 552), -aluminate (Weinland, Lang, and Fikentscher, *Z. anorg. Chem.*, 1925, **150**, 47), -borate (Funk and Binder, *ibid.*, 1926, **159**, 121), -beryllate (Ray, *ibid.*, 1931, **201**, 289), and -germanate (Dennis, Staneslow, and Forgeng, *J. Amer. Chem. Soc.*, 1933, **55**, 4392). No such compounds of tin, antimony, or bismuth have been described, though these metals are known to form anionic complex fluorides with both uni- and bi-valent cations (Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans Green and Co., London, 1927, Vol. VII, p. 422; 1929, Vol. IX, pp. 465, 659).

Chlorostannates of hydrazine, and of some of its condensation products with ketones, have been described (Pugh and Stephen, *locc. cit.*), and the present paper records the results of attempts to make similar fluoro-salts of tin, arsenic, antimony, and bismuth. The compounds described are hydrazinium hydrogen tetrafluorostannite, hydrazinium hexafluoroantimonate, hydrazinium hydrogen pentafluoroantimonite, hydrazinium hydrogen pentafluorobismuthite, and dihydrazinium hexafluorostannate. They were made by crystallisation of the mixed component fluorides from aqueous solutions, though better results were obtained from aqueous acetone in some cases. The fluoro-bismuthite, however, was made by prolonged digestion of bismuth trifluoride with hydrazine dihydrofluoride solution. Attempts to crystallise fluoroarsenites were unsuccessful, for though arsenious oxide dissolves readily in warm solutions of hydrazine dihydrofluoride the only solid recovered by evaporation at room temperature was the latter component. The fluoroarsenite ion, if it exists in solution, is too unstable, and arsenic volatilises completely as the trifluoride.

It is significant that, although crystallisation of the mixed chlorides of hydrazine and tin from aqueous acetone (*idem, loc. cit.*) yields dimethylketazinium chlorostannate (and further work, yet unpublished, has shown that similar chloroantimonites and chlorobismuthites can be prepared), yet crystallisation of the mixed fluorides, under the same conditions, yields the unchanged hydrazinium complex salt. There is, however, some evidence, *e.g.*, liberation of heat, that condensation does take place when the mixed fluoride solutions are treated with acetone, and it is possible that ketazinium fluoro-salts do exist in solution. They do not, however, separate in the solid phase.

EXPERIMENTAL

Analytical Methods.—Metals were determined by weighing the oxides after repeated evaporation with nitric acid and ignition; fluoride was determined, after removal of the metal as sulphide, by titration with thorium nitrate (Rowley and Churchill, *Ind. Eng. Chem. Anal.*,

* The papers, *J.*, 1952, 4138, and *J.*, 1953, 354, are considered as Parts I and II, respectively.

1937, **9**, 551); hydrazine was determined by titration with iodate (Andrews's method). In the fluoro-stannites and -antimonites, the anions of which also consume iodate, a total iodate titre was determined on one sample, and then a second iodate titre, determined on another sample after removal of the metal as sulphide, gave the hydrazine titre alone; this procedure provided a check on the results for both hydrazine and metal.

Dihydrazinium Hexafluorostannate.—Stannic chloride pentahydrate (12 g.) was dissolved in hot distilled water, and ammonia solution was added until the mixture was alkaline to methyl-orange. The stannic hydroxide was filtered off, washed with hot water until free from chloride, and dissolved in a small excess of 40% hydrofluoric acid. Other methods of making stannic fluoride solutions, *e.g.*, evaporation of stannic chloride with hydrofluoric acid, were tedious. The solution was then treated with hydrazine hydrate (12 c.c.; 28%), previously made acid with hydrofluoric acid, and evaporated to crystallisation. The first crop of crystals was contaminated with hydrazine dihydrofluoride, but subsequent crops were reasonably pure. Recrystallisation from acetone–water (4 : 1) by slow evaporation gave large flat plates, d_{22}^{22} 2·57, m. p. 194—196° (decomp.) [Found: N_2H_4, 21·3; F, 37·9; Sn, 39·8. $(N_2H_5)_2SnF_6$ requires N_2H_4, 21·4; F, 38·2; Sn, 39·8%]. The *salt* is non-hygroscopic, yet it attacks glass. It decomposes with effervescence when heated above its m. p., the vapours smelling strongly of hydrazine. It is insoluble in ether, ethanol, acetone, chloroform, benzene, or light petroleum, but freely soluble in water, yielding clear solutions which do not immediately afford a precipitate with hydrogen sulphide: precipitation is complete only after repeated filtration and re-saturation in hot solution. Stannic hydroxide is, however, completely precipitated by ammonia. Much heat is evolved when concentrated solutions are mixed with acetone but the salt is recovered unchanged on cooling or on evaporation; it has not been possible to prepare ketazinium and hydrazonium fluorostannates analogous to the chlorostannates previously described (*idem, loc. cit.*).

The crystals are monoclinic. They are generally flat quadrangular (010) plates with angles of 75° and 105°, often elongated parallel to *c* and showing (100) with prism and other faces. No pronounced cleavage. Lamellar twinning common. Optically negative, negative elongation. $\widehat{Xc} = 20°$. $2V^{\alpha}(D) = 17\frac{1}{2}°$. Dispersion of the optic axes is extreme, with red > violet, giving rise to incomplete extinction and abnormal interference colours in white light. n_D: α 1·442, β 1·451, γ 1·453, γ − α 0·011.

Hydrazinium Hydrogen Tetrafluorostannite.—Freshly precipitated stannous hydroxide, made from stannous chloride dihydrate (11·3 g.) by precipitation with ammonia as described above for stannic hydroxide, was dissolved in a solution of hydrofluoric acid (10 g.; 40%) and hydrazine hydrate (13 g.; 28%). Rapid evaporation on the water-bath yielded needles which, after drying on paper and then *in vacuo*, had d_{23}^{23} 3·09, m. p. 117—118° (Found: N_2H_4, 13·9; F, 33·0; Sn, 51·8. $N_2H_5.HSnF_4$ requires N_2H_4, 14·0; F, 33·2; Sn, 51·9%). The *salt* is non-deliquescent and is not unduly oxidised by air when dry. Its solutions in water, however, are rapidly oxidised, so the preparation and crystallisation must be carried out as expeditiously as possible. Continued exposure of acid solutions yielded crystals of pure dihydrazinium hexafluorostannate. Like the latter, it is insoluble in the common organic solvents.

The crystals belong to the orthorhombic system. They are colourless, elongated pinacoidal plates with pronounced cleavages parallel to the elongation direction. The optic axial plane is parallel to the elongation direction, with $Bx^{\circ}(\alpha)$ emerging normal to the plane of the plates. Elongation positive. Optically negative. $2V^{\alpha}(D) = 65°$. Dispersion strong, red > violet. n_D: α 1·570, β 1·633, γ 1·647. Birefringence high; γ − α 0·077.

Hydrazinium Hexafluoroantimonate.—Antimony pentachloride (16 g.) was added slowly to water (200 c.c.) at 0° and the hydrated antimony pentoxide, after being washed free from chloride, was dissolved in hydrofluoric acid (20 g.; 40%) containing hydrazine hydrate (10 g.; 28%). The liquid was concentrated to about half bulk on the water-bath and was then kept for several days over solid sodium hydroxide. At no stage was there any evidence, *e.g.*, evolution of nitrogen, of oxidation–reduction. The large dense crystals were dried on filters and *in vacuo* (Found: N_2H_4, 11·2; Sb, 42·6. $N_2H_5SbF_6.H_2O$ requires N_2H_4, 11·2; Sb, 42·5%). The determination of antimony in this *salt* was troublesome. Precipitation with hydrogen sulphide, even after preliminary boiling with sodium hydroxide, was slow and incomplete; reduction in boiling solution with sulphurous acid, with zinc, or with aluminium, was also slow and incomplete after an hour. The methods finally adopted involved the removal of fluoride either by evaporation to fumes with sulphuric acid, or by repeated evaporation with nitric acid. In the former procedure, the antimony was subsequently reduced with sulphurous acid and

titrated with standard permanganate (Pugh, *J.*, 1933, 1); in the latter, the residue was ignited and weighed as antimony tetroxide. The two methods gave identical results.

The salt is deliquescent and exceedingly soluble in water but insoluble in common organic solvents. It dissolves partially in its water of crystallisation at 50° and dissolution (or melting) is complete at 75°.

The crystals, probably orthorhombic, are colourless, pinacoidal plates with no pronounced cleavage. Optically negative. $2V^{\alpha}(D) = 57°$. Dispersion strong, red < violet. n_D: α 1·423, β 1·436, γ 1·445.

Hydrazinium Hydrogen Pentafluoroantimonite.—Antimony trioxide (6 g.) was dissolved in hydrofluoric acid (6 g.; 40%), and the solution was treated with hydrazine hydrate (6 c.c.; 28%) previously neutralised with hydrofluoric acid. The complex separated on cooling and the liquid yielded a further crop on concentration. Recrystallisation from water or from aqueous acetone yielded needles, with d_{26}^{26} 3·15 and m. p. 94—95° (Found: N_2H_4, 12·7; F, 37·7; Sb, 48·7. $N_2H_5HSbF_5$ requires N_2H_4, 12·8; F, 37·9; Sb, 48·6%). The *salt* is non-hygroscopic but is freely soluble in water, forming clear and stable solutions. This complex anion is not as stable as the hexafluoroantimonate ion, its solutions being readily and completely decomposed by hydrogen sulphide. The salt is insoluble in the organic solvents quoted earlier.

The crystals are monoclinic; (010) pinacoids elongated parallel to *c* and often terminated by domes or pyramids. The optic axial plane is parallel to (010). $\widehat{Xc} = 20°$. Elongation negative; optically negative. $2V^{\alpha}(D) = 21°$. Dispersion strong, red > violet, giving abnormal interference tints near the extinction position for white light. n_D: α 1·540, β 1·588, γ 1·595. Birefringence high: $\gamma - \alpha$ 0·055.

Hydrazinium Hydrogen Pentafluorobismuthite.—Bismuth trioxide (5 g.) was dissolved in the minimum amount of dilute nitric acid, and hydrofluoric acid added until precipitation was complete. The bismuth fluoride, after being washed with water to remove nitric acid, was digested on the water-bath for an hour with hydrazine dihydrofluoride (2 g.), and the insoluble product was washed, dried, ground well, and re-digested in the same way. Repetition of this process yielded a crystalline powder of constant composition and d_{26}^{26} 4·43 (Found: N_2H_4, 9·4; F, 28·3; Bi, 62·0. $N_2H_5,HBiF_5$ requires N_2H_4, 9·5; F, 28·1; Bi, 61·8%). Although this *complex* is almost insoluble in water, all attempts to make it by precipitation from bismuth salt solutions with hydrazine fluoride–hydrofluoric acid solutions yielded mixtures of the complex and bismuth trifluoride. Similar mixtures were obtained when freshly precipitated bismuth hydroxide was added as a slurry to solutions of hydrazine fluoride in excess of hydrofluoric acid. Long digestion of these mixtures was necessary to effect complete recrystallisation of the fluoride in the form of the complex.

The salt decomposes when heated, without melting, yielding a white sublimate, vapours of hydrofluoric acid, and a black residue of metallic bismuth. It is soluble in acids and insoluble in organic solvents.

The crystals are orthorhombic or monoclinic, being minute, colourless scales with six-sided outline and perfect cleavage parallel to the surface. Optically positive. $2V^{\gamma} = 72°$ (calc.). The plates give centred, or near-centred optic normal figures, suggesting orthorhombic symmetry. n_D: α 1·603, β 1·615, γ 1·638. $\gamma - \alpha$ 0·035.

Attempts to Prepare Hydrazinium Fluoroarsenite.—Arsenious oxide (6 g.) dissolved readily in a mixture of hydrofluoric acid (15 g.; 33%) and hydrazine hydrate (12 g.; 28%), the liquid smelling strongly of arsenic trifluoride. However, hydrazine dihydrofluoride (4 g.) separated on cooling, the crystals being contaminated with arsenious oxide (Found: N_2H_4, 43·0; F, 51·0; As, 2·1. Calc. for $N_2H_6F_2$: N_2H_4, 44·5; F, 52·9%). Evaporation at room temperature yielded further crystals of similar composition, and neighbouring objects became coated with arsenious oxide dust. The whole of the hydrazine used originally was recovered as dihydrofluoride, but only a small fraction of the arsenic was recovered. Arsenic trifluoride evidently volatilised, and was hydrolysed in moist air. H. von Helmolt (*Z. anorg. Chem.*, 1893, **3**, 115) found that arsenious oxide dissolved in ammonium fluoride solutions, and he was likewise unable to prepare ammonium fluoroarsenite.

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398. *The Hofmann Reaction with α- and β-Hydroxy-amides: Reactions of the Intermediate* iso*Cyanates.*

By C. L. Arcus and D. B. Greenwood.

A mechanism for the (Weerman) degradation of an α-hydroxy-amide R·CH(OH)·CO·NH_2 is proposed in which the aldehyde R·CHO is formed by the elimination of cyanate ion from the intermediate anion $^-$O·CHR·NCO.

Methyl *N*-1-methoxyethylcarbamate has been prepared; its acidic hydrolysis yields acetaldehyde, carbon dioxide, and ammonia, but not methylamine.

Salicylamide with hypochlorite in strongly alkaline solution yields 4 : 5-benzoxazol-2-one (Graebe and Rostovzeff, *Ber.*, 1902, **35**, 2747), but in less basic solutions 5- and 3-chloro-2-hydroxybenzamides are formed; the mechanism of the reaction is discussed.

β-Hydroxy-β-phenylpropionamide with bromine and methanolic sodium methoxide yields 5-phenyloxazolid-2-one.

The main characteristics of the Hofmann reaction with different types of hydroxy-amide are already known, but the mechanisms of a number of reactions within this field have not been fully elucidated; several such reactions have now been investigated.

It has been established (Ault, Haworth, and Hirst, *J.*, 1934, 1722; Haworth, Peat, and Whetstone, *J.*, 1938, 1975) that the reaction of aqueous hypochlorite and alkali with an α-hydroxy-amide yields the aldehyde together with the cyanate ion (1), and that a similar reaction with an α-methoxy-amide yields the aldehyde and ammonia, but no cyanate (2). Ault *et al.* consider that in (2) the hydrolysis of the *iso*cyanate proceeds *via*

$$\text{R·CH(OH)·CO·NH}_2 \xrightarrow{\text{NaOCl}} \text{R·CH(OH)·NCO} \xrightarrow{\text{NaOH}} \text{R·CHO} + \text{NaCNO} \quad . \quad . \quad (1)$$

$$\text{R·CH(OMe)·CO·NH}_2 \xrightarrow{\text{NaOCl}} \text{R·CH(OMe)·NCO} \xrightarrow{\text{NaOH}} \text{R·CHO} + \text{MeOH} + \text{Na}_2\text{CO}_3 + \text{NH}_3 \quad . \quad (2)$$

the carbamate (I; R′ = Na), a conclusion supported by the observation that benzaldehyde and ammonia are formed quantitatively by alkaline hydrolysis of methyl *N*-α-methoxybenzylcarbamate (I; R = Ph, R′ = Me). These authors suggest that in (1) "the formation of a co-ordinated intermediate product (II), in place of a carbamic acid, is responsible for the marked difference in the character of the end products." It is now

$$\text{R·CH(OMe)·NH·CO}_2\text{R}' \qquad \text{R·CH(OH)(NCO)} \quad \text{(II)}$$
(I)

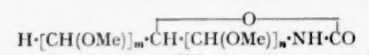
suggested that (1) proceeds by an elimination mechanism: the electron-attracting *iso*cyanate group renders the hydroxyl-hydrogen atom weakly acidic, and the anion (III) is formed either by direct ionisation or by the attack of a hydroxyl ion, electronic movements as shown then yielding the aldehyde and cyanate ion:

$$\text{HO}^- + \text{R·CH(OH)·N=C=O} \longrightarrow \text{H}_2\text{O} + \text{R·CH(O}^-\text{)·N=C=O} \longrightarrow \text{R·CHO} + \text{NCO}^-$$
(III)

Methylation of the hydroxyl group renders this process impossible, in accordance with the experimental finding.

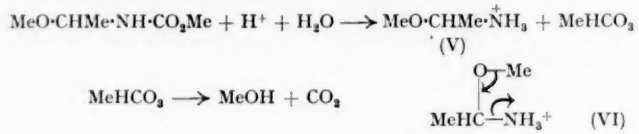
Haworth *et al.* (*loc. cit.*), following earlier work by Irvine and Pryde (*J.*, 1924, **125**, 1945) and Humphreys, Pryde, and Waters (*J.*, 1931, 1298), isolated the cyclic urethanes (IV; $m = n = 2$; and $m = 1$, $n = 3$) from the reaction of aqueous hypochlorite with

2 : 3 : 5 : 6- and 2 : 3 : 4 : 6-tetramethylgluconamide; these compounds respectively contain a 6- and a 7-membered ring formed by intramolecular reaction between a hydroxyl and an *iso*cyanate group. The reaction with 3 : 5 : 6-trimethylgluconamide, which bears hydroxyl groups at $C_{(2)}$ and $C_{(4)}$, yielded 2 : 4 : 5-trimethylarabinose and cyanate; no cyclic urethane could be isolated. It is inferred from this result that elimination *via* (III) is more rapid than urethane formation.



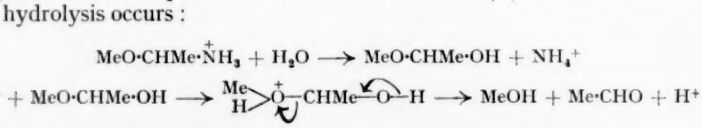
(IV)

Methyl *N*-1-methoxyethylcarbamate (I; R = R′ = Me) has been prepared by the reaction of α-methoxypropionamide with bromine and methanolic sodium methoxide. Acidic hydrolysis of this carbamate yielded acetaldehyde, and nearly the theoretical quantities of carbon dioxide and ammonia; methylamine was absent. The following course for the hydrolysis appears to be the most probable. The amido-link is first hydrolysed :



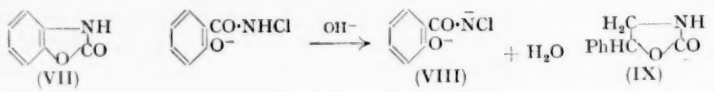
(V) (VI)

Since methylamine is not a product of the reaction the ion (V) does not react as in (VI), and further hydrolysis occurs :



Graebe and Rostovzeff (*Ber.*, 1902, **35**, 2747), by the action of sodium hypochlorite (2 mols.) and sodium hydroxide (4·5 mols.) on salicylamide, obtained 4 : 5-benzoxazol-2-one (VII); this preparation has been repeated. Further, it has been found that the interaction of equimolar quantities of hypochlorite and salicylamide yields 5- and 3-chloro-2-hydroxybenzamides; no (VII) was isolated. Reaction in the presence of two mols. of alkali gave a similar result. It is concluded that the anion of the *N*-chloroamide (VIII), the essential precursor to the Hofmann rearrangement, is formed only when the hydroxyl-ion concentration is high, electron-release from the existing phenoxide ion opposing the removal of a second proton. The Hofmann reaction is therefore inhibited in solutions which are not strongly alkaline, and substitution (by hypochlorous acid, hypochlorite ion, or chloramine) then occurs in the nucleus.

Reaction of β-hydroxy-β-phenylpropionamide with bromine and methanolic sodium methoxide yielded the 5-membered cyclic urethane, 5-phenyloxazolid-2-one (IX), a result analogous to the formation of (VII) and of the 6- and 7-membered cyclic urethanes (IV; $m = n = 2$) and (IV; $m = 1, n = 3$).



(VII) (VIII) (IX)

Experimental

Amides were prepared by the reaction of esters with ammonia under the conditions described in the first preparation.

Ethyl α-methoxypropionate (51 g.; Nieman, Benson, and Read, *J. Org. Chem.*, 1943, **8**, 397) and ammonia (*d* 0·88; 300 ml.) were shaken mechanically in a stoppered bottle; when the mixture had become homogeneous it was kept for 10 days and then evaporated under reduced pressure. The distilled product, b. p. 111°/18 mm., was recrystallised from benzene–*cyclo*hexane and yielded α-methoxypropionamide (42 g.), m. p. 81° (Found, by hydrolysis with aqueous-alcoholic 0·5N-potassium hydroxide: equiv., 101. Calc. for $C_4H_9O_2N$: equiv., 103). Gauthier (*Ann. Chim.*, 1909, **16**, 315) records m. p. 81°.

Ethyl salicylate (70 g.), with ammonia (400 ml.) and ethanol (60 g.) for 6 days, yielded salicylamide (54 g., from benzene–acetone), m. p. 137°.

Ethyl β-hydroxy-β-phenylpropionate (10·5 g.; Hauser and Breslow, *Org. Synth.*, 1941, **21**, 51), with ammonia (150 ml.) for 2 days, yielded β-hydroxy-β-phenylpropionamide (8·9 g., from chloroform–ethanol), m. p. 122—123°. Posner (*Ber.*, 1905, **38**, 1129) records m. p. 122—123°.

Methyl N-1-*Methoxyethylcarbamate.*—Sodium (4·7 g.) was allowed to react with dry methanol (100 ml.) and to the solution, cooled in ice, was added α-methoxypropionamide (10·3 g.) in methanol (30 ml.); bromine (16·3 g.) was added dropwise with stirring, the mixture being kept below 2°. It was then heated under reflux for 15 min., cooled, and made neutral to phenolphthalein with glacial acetic acid, and the methanol distilled off through a short column; the residue was extracted with ether. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated. The product on distillation yielded *methyl* N-1-*methoxyethylcarbamate* (7·3 g.), b. p. 77°/16 mm., n_D^{25} 1·4241 (Found: C, 45·4; H, 8·2; N, 10·2. $C_5H_{11}O_3N$ requires C, 45·1; H, 8·3; N, 10·5%).

Hydrolyses. Methyl *N*-1-methoxyethylcarbamate (1·5 g.) was weighed into a flask which was then connected to two traps, the first cooled in ice, the second with solid carbon dioxide. The second trap was connected to a calcium chloride-filled U-tube which had been saturated with carbon dioxide and purged with hydrogen, a weighed U-tube the first two-thirds of which were filled with soda-lime and the last third with calcium chloride, and finally to a soda-lime guard tube. 4N-Sulphuric acid (40 ml.) was run into the flask which was then heated with steam. Carbon dioxide-free hydrogen was passed through the apparatus during the hydrolysis, which was allowed to proceed for 4 hr., by which time the weight of the central tube (after it had been purged with carbon dioxide-free air) had become constant. In a control experiment with sodium hydrogen carbonate, 98% of the theoretical quantity of carbon dioxide was collected. An aliquot of the hydrolysis solution (which gave no carbylamine with chloroform and alkali) was used for a Kjeldahl determination of ammonia. The following tests were applied to the ammonium chloride obtained on evaporation: (*a*) it was insoluble in hot absolute alcohol; (*b*) the filtrate from extraction with 96% alcohol gave no colour with 2 : 4-dinitrochlorobenzene, or when warmed to 75° with tetrachloroquinone. Methylamine was therefore absent. From the contents of the traps there was prepared a semicarbazone having m. p. 160° alone and when mixed with authentic acetaldehyde semicarbazone of m. p. 161—162°, and a dimedone derivative having m. p. 139° alone and when mixed with authentic acetaldehyde–dimedone compound having m. p. 139°. There were obtained carbon dioxide (i) 105, (ii) 100%, and ammonia (i) 94, (ii) 96% of the theoretical quantities.

The hydrolysis of methyl *N*-1-methoxyethylcarbamate (2·66 g.) with 1·5N-sodium hydroxide (200 ml.) for 1½ hr. at 50° and finally at 95° (the absorption tubes were omitted) yielded a tar (0·46 g.) and, in the colder trap, a solid which decomposed at 70° to ammonia and acetaldehyde; these products were presumed to be, respectively, acetaldehyde resin and acetaldehyde-ammonia. A portion of the hydrolysis solution was treated with pyridine, sufficient acetic acid to render the mixture acid, chloroform, and 1% aqueous copper sulphate: the chloroform layer developed no blue colour, whence cyanate was absent.

Salicylamide–Hypochlorite Reactions.—(*a*) Salicylamide (3·0 g.) yielded, by Graebe and Rostovzeff's method (*loc. cit.*), a product, the benzene solution of which was heated with charcoal at 65° for 1 hr.; on cooling there separated 4 : 5-benzoxazol-2-one (1·0 g.), colourless crystals, m. p. 140—141° (these authors record m. p. 138—139°). Admixture with salicylamide depressed the m. p. by 40°.

(*b*) A solution of salicylamide (16·4 g.) in water (50 ml.) was cooled to 0°, 0·92M-sodium hypochlorite (130 ml.) was added with stirring during ¾ hr., and the mixture was heated on a steam-bath for ¾ hr. Next day the solution was saturated with carbon dioxide, which precipitated amides (13·9 g.); acidification with hydrochloric acid yielded a precipitate (2·0 g.) which after recrystallisation from water had m. p. 157° alone and when mixed with salicylic acid. The amides were fractionally crystallised from aqueous dioxan and yielded 5-chloro-2-hydroxybenzamide (3·5 g.), m. p. 227—228° (Found: C, 49·2; H, 3·5; N, 8·0; Cl, 20·4. Calc. for $C_7H_6O_2NCl$: C, 49·0; H, 3·5; N, 8·2; Cl, 20·7%) (Biltz and Stepf, *Ber.*, 1904, **37**, 4024, record m. p. 226—227°), and 3-chloro-2-hydroxybenzamide (7·5 g.), m. p. 183—184° (Found: C, 49·0; H, 3·7; N, 7·9; Cl, 20·1%) (Hirwe, Rana, and Gavankar, *Proc. Indian Acad. Sci.*, 1938, **8**, *A*, 208, record m. p. 174—175°).

(*c*) Salicylamide (2·0 g.), 0·87M-sodium hypochlorite (18 ml.), and 0·88N-sodium hydroxide (34 ml.) were allowed to react as in (*b*). The solution was then progressively acidified with hydrochloric acid, and material which separated was removed, as follows: to pH 8·5, a

precipitate which after recrystallisation from benzene–dioxan had m. p. 225—227° alone and m. p. 226—227° when mixed with 5-chloro-2-hydroxybenzamide from (*b*); to pH 6·8, material m. p. 170—194°; to pH 2, an oil of b. p. approx. 240°, which solidified and appeared to be chlorophenol(s).

5-Phenyloxazolid-2-one.—Bromine (4·2 g.) was allowed to react with β-hydroxy-β-phenylpropionamide (4·1 g.) and methanolic sodium methoxide (from 1·2 g. of sodium and 150 ml. of methanol) by the procedure used for the preparation of methyl *N*-1-methoxyethylcarbamate; the mixture was heated under reflux for ¾ hr. and then made neutral to phenolphthalein with glacial acetic acid, and the greater part of the methanol was distilled off. Ether was added to the residue, the precipitated sodium bromide was filtered off, and the solvents were distilled; the product, after warming in aqueous solution with charcoal and recrystallisation from water, yielded *5-phenyloxazolid-2-one* (2·0 g.), m. p. 89—90° (Found: C, 65·8; H, 5·5; N, 8·7. $C_9H_9O_2N$ requires C, 66·2; H, 5·6; N, 8·6%). Schroeter (D.R.-P. 220,852) who prepared this compound by heating β-hydroxy-β-phenylpropionyl azide, records m. p. 87—88·5°, but no analysis. 5-Phenyloxazolid-2-one (0·28 g.) was heated on a steam-bath for 1½ hr. with 4N-sodium hydroxide (3 ml.); drops of oil separated. To the cold mixture, benzoyl chloride (0·25 g.) was added with shaking. The product was next day filtered off and after recrystallisation from aqueous alcohol yielded 2-benzamido-1-phenylethanol (0·26 g.), m. p. 147·5—148·5°. Rosenmund (*Ber.*, 1913, **46**, 1046) and Wolfheim (*Ber.*, 1914, **47**, 1440) record m. p. 147° and 148—149·5° respectively.

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BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March 10th*, 1953.]

NOTES.

399. *The Preparation of* 1-p-*Diphenylylethyleneimine.*

By J. N. BAXTER and J. CYMERMAN-CRAIG.

IN view of the cytotoxic and tumour-inhibiting properties of certain ethyleneimines (Hendry, Homer, Rose, and Walpole, *Brit. J. Pharmacol.*, 1951, **6**, 357) 1-*p*-diphenylylethyleneimine was prepared; it will be examined for carcinogenic properties by Dr. A. L. Walpole (Dr. F. L. Rose, personal communication).

The only 1-arylethyleneimines reported in detail are 1 : 2 : 3-triphenyl- (Taylor, Owen, and Whittaker, *J.*, 1938, 206) and 1-*p*-(*p'*-aminophenylsulphonyl)phenyl-ethyleneimine (Jackson, *J. Org. Chem.*, 1951, **16**, 1899). Reaction of 4-aminodiphenyl with 2-bromoethanol gave 4-bis-2'-hydroxyethylaminodiphenyl (Ross, *J.*, 1949, 183), with small amounts of 2-*p*-diphenylylaminoethanol (unpublished observations). The required 2-*p*-diphenylylaminoethanol was obtained in 36% yield by the action of 2-bromoethanol on 4-benzylideneaminodiphenyl followed by hydrolysis of the intermediate quaternary salt (cf. Decker and Becker, *Annalen*, 1913, **395**, 362). Many attempts to improve the yield gave much unchanged Schiff's base, together with 4-aminodiphenyl. Attempted isolation of the intermediate quaternary salt resulted in quantitative transformation into 4-diphenylylammonium bromide; instability of the intermediate quaternary compounds in this reaction has been noted previously (Hantzsch and Schwab, *Ber.*, 1901, **34**, 837; Knoevenagel, *ibid.*, 1923, **55**, 1921).

With 48% hydrobromic acid the alcohol readily gave the desired 2-*p*-diphenylylaminoethyl bromide; this and its hydrobromide showed evidence of chemical change on repeated recrystallisation.

Treatment of the base with methanolic sodium methoxide (1 mol.) afforded 1-*p*-diphenylylethyleneimine in excellent yield. When heated or repeatedly recrystallised this was partly transformed into a high-melting solid; the ease of polymerisation of ethyl-

eneimines is well known. The ethyleneimine readily gave 2-*p*-diphenylylaminoethyl chloride hydrochloride, identical with a sample prepared by the action of thionyl chloride on 2-*p*-diphenylylaminoethanol. The dimer, 1 : 4-bis-*p*-diphenylylpiperazine, was prepared from 4-bis-2′-chloroethylaminodiphenyl and 4-aminodiphenyl by Davis and Ross' method (*J.*, 1949, 2831).

Experimental.—2-p-*Diphenylylaminoethanol.* 4-Benzylideneaminodiphenyl (12·8 g., 0·05 mol.), suspended in absolute alcohol (150 c.c.) containing 2-bromoethanol (5 c.c., 0·075 mol.), was heated for 2·5 hours under reflux. The solution was cooled to 0° and unchanged Schiff's base filtered off (7·2 g., 56%). The filtrate was boiled with hydrochloric acid (100 c.c.; 3N) for 0·5 hour, alcohol being allowed to distil off. The cooled solution was extracted with ether to remove benzaldehyde, and the amine was then liberated with sodium hydroxide and extracted with ether. The residue, after removal of solvent from the dried (Na_2SO_4) extracts, was recrystallised from light petroleum (b. p. 60—90°), giving 2-p-*diphenylylaminoethanol* as needles, m. p. 112° (1·55 g., 36% calc. on Schiff's base which reacted) (Found: C, 78·6; H, 6·95; N, 6·4. $C_{14}H_{15}ON$ requires C, 78·85; H, 7·1; N, 6·55%). The mother-liquors contained some 4-aminodiphenyl isolated as the hydrochloride (1·15 g.). 2-p-*Diphenylylaminoethanol hydrochloride* crystallised from ethyl acetate in needles, m. p. 152—153° (Found: N, 5·6. $C_{14}H_{15}ON,HCl$ requires N, 5·65%).

Attempted isolation of N-*benzylidene*-N-2′-*hydroxyethyl*-4-*diphenylylammonium bromide.* The quaternary salt (m. p. >310°), obtained by addition of ether to the filtrate after removal of Schiff's base from an experiment as above, liberated benzaldehyde on treatment with dilute acid; it was transformed by repeated crystallisation from methanol–ether into 4-*diphenylylammonium bromide*, m. p. 340° (decomp.) (Found: C, 57·7; H, 4·65: N, 5·4; Br, 31·5. $C_{12}H_{11}N,HBr$ requires C, 57·6; H, 4·85; N, 5·6; Br, 31·95%), identified as the benzenesulphonate, m. p. and mixed m. p. 284° (Bauer and Cymerman, *J.*, 1950, 1826).

2-p-*Diphenylylaminoethyl bromide.* A solution of 2-*p*-diphenylylaminoethanol (2·94 g.) in hydrobromic acid (22 c.c.; 48%) was refluxed for 6 hours; 10 c.c. of distillate were then removed and the residual solution refluxed for a further 4 hours. The cooled solution was poured into ice-water and filtered, and the product washed with ice-water, alcohol, and ether, giving plates (4·49 g., 89%), m. p. 192—195°. Crystallisation from *iso*propanol gave plates, m. p. 196—197°, of 2-p-*diphenylylaminoethyl bromide hydrobromide* (Found: C, 47·1; H, 4·45. $C_{14}H_{14}NBr,HBr$ requires C, 47·1; H, 4·25%). The substance appeared to undergo some solvolysis on recrystallisation.

The free base, liberated with dilute ammonia and crystallised from light petroleum (b. p. 60—90°), gave 2-p-*diphenylylaminoethyl bromide*, prisms, m. p. 75—76° (Found: N, 5·5. $C_{14}H_{14}NBr$ requires N, 5·1%). Repeated recrystallisation caused the formation of a high-melting impurity, insoluble in light petroleum.

1-p-*Diphenylylethyleneimine.* A solution of 2-*p*-diphenylylaminoethyl bromide (1·12 g.) in methanol (100 c.c.) was treated with methanolic sodium methoxide until just alkaline to brilliant-yellow. The mixture was refluxed for 2·5 hours, filtered from sodium bromide, and evaporated to dryness. The washed (water) and dried (P_2O_5) residue (0·74 g., 93%) had m. p. 91—92° and on crystallisation from light petroleum (b. p. 40—60°) gave 1-p-*diphenylylethyleneimine* as prisms, m. p. 98—99° (Found: C, 86·05; H, 6·85; N, 6·95. $C_{14}H_{13}N$ requires C, 86·15; H, 6·7; N, 7·15%). Repeated recrystallisation gave increasing amounts of a high-melting, petrol-insoluble impurity.

2-p-*Diphenylylaminoethyl chloride.* (*a*) A solution of 1-*p*-diphenylylethyleneimine (0·13 g.) in dry ether was saturated with hydrogen chloride gas. The precipitate (0·12 g., 67%; m. p. 173—175°) crystallised from methanol–ether in prisms, m. p. 176—178°, of 2-p-*diphenylylaminoethyl chloride hydrochloride* (Found: C, 62·8; H, 5·8; N, 5·5. $C_{14}H_{14}NCl,HCl$ requires C, 62·7; H, 5·65; N, 5·25%). The mother-liquors contained a high-melting by-product (0·02 g.).

(*b*) A solution of 2-*p*-diphenylylaminoethanol (0·13 g.) in dry chloroform (10 c.c.) was refluxed with thionyl chloride (0·5 c.c.) for 0·5 hour. Evaporation to dryness *in vacuo* and trituration of the residue with dry ether gave a hydrochloride (0·085 g., 52%), m. p. 175—177°, undepressed on admixture with the material prepared as in (*a*) above.

1 : 4-*Bis*-p-*diphenylylpiperazine.* A solution of 4-aminodiphenyl (5 g., 0·03 mol.) and 4-bis-2′-chloroethylaminodiphenyl (2·95 g., 0·01 mol.) in 50% aqueous acetone (1100 c.c.) was refluxed for 4 hours, during which crystals separated. The hot solution (A) was filtered, and the crude product (2·3 g.) extracted with ether (100 c.c.). The ether-insoluble portion (1·05 g., 16%) was the *piperazine*, m. p. 305·5—306°, crystallising from toluene in plates of unchanged

m. p. (Found: N, 7·15. $C_{28}H_{26}N_2$ requires N, 7·15%). Evaporation of the filtrate (A) gave a further 0·1 g. (2·5%) of the piperazine, m. p. 300°.

Thanks are offered to Mrs. E. Bielski and the C.S.I.R.O. microanalytical laboratory for microanalyses. One of us (J. N. B.) is indebted to the University of Sydney for the award of a Monsanto (Aust.) Pty. Ltd. Scholarship.

ORGANIC CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY. [*Received, December 10th*, 1952.]

400. *The Determination of C-Methyl Groups in Some Unsaturated Straight-chain Compounds.*

By A. D. CAMPBELL and V. J. CHETTLEBURGH.

CAMPBELL and MORTON (*J.*, 1952, 1693) showed that the Kuhn–Roth procedure for the determination of *C*-methyl groups is a unreliable method for branched-chain fatty acids. In the terpene series, side-chains attached to *cyclo*alkanes give low yields of acetic acid but when attached to *cyclo*alkenes, cyclic alcohols, and ketones give high yields (Petru, Jurecek, and Kovar, *Chem. Listy*, 1951, **45**, 300; *Chem. Abs.*, 1952, **46**, 4506), and some compounds containing a polymethylene chain but initially no *C*-methyl group have been found to give a positive *C*-methyl value (W. Baker, personal communication).

The modified Kuhn–Roth procedure (Ginger, *J. Biol. Chem.*, 1944, **156**, 452) when applied to some unsaturated straight-chain compounds has given anomalous yields of acetic acid. Our results (on 10—12-mg. samples by Campbell and Morton's procedure) were: oleic acid, 1·37, 1·43, 1·28*; methyl oleate, 1·36, 1·33; oleyl alcohol, 1·53; linoleic acid, 1·29, 1·16 (yields expressed as moles of acetic acid per mole of compound) (* digested in a sealed tube at 100° for 2 hr.).

In these cases the Kuhn–Roth precedure, when applied to unsaturated straight-chain compounds, gives entirely misleading results. As the yield of acetic acid per *C*-methyl group in branched chain fatty acids may be as low as 62% the above results are those which would be expected from a compound containing two *C*-methyl groups. Saturated dibasic acids such as azelaic, glutaric, and malonic acid did not give a *C*-methyl value.

We thank Mr. R. P. Hansen, Fats Research Laboratory, Wellington, for supplying pure samples of methyl oleate and linoleic acid.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, January 8th*, 1953.]

401. *The Alkaloids of* Senecio ruwenzoriensis.

By M. L. SAPIRO.

EXTRACTION of the plant *Senecio ruwenzoriensis* from the Nanyuki district of Kenya, where it has been suspected of causing poisoning of cattle, has yielded two new alkaloids, which have been named ruzorine and ruwenine.

Preliminary small-scale extraction in the cold yielded 0·38% of alkaloids; but extraction of 3 kg. of dry plant by Koekemoer and Warren's method (*J.*, 1951, 66) gave only 0·11% of ruwenine, of which one-tenth was from the reduction stage (*loc. cit.*) and 0·034% of ruzorine. The low yields in this process were due to the relative instability of the alkaloids.

Experimental.—M. p. and decomposition temperatures are corrected, a standard rate of heating, 2° per min., being adopted.

Separation and purification. The crude mixture obtained in the extraction process was treated with very dilute sulphuric acid and the extract, after filtering, was rendered alkaline with ammonia and re-extracted with chloroform. After removal of the chloroform the residue was treated with cold acetone. Ruzorine remained undissolved and was crystallised from

pyridine and washed with acetone or peroxide-free ether. Ruwenine, extracted by acetone, was freed from decomposition products *via* the sulphate or hydrochloride and crystallised from methanol.

Ruzorine formed colourless prisms or needles, m. p. 161—163° (decomp. from 134°), very soluble in water, soluble in the usual organic solvents except ether, ethyl acetate, or acetone (Found: C, 56·2, 55·9; H, 7·4, 7·35; N, 3·9, 3·65. $C_{18}H_{27}O_8N$ requires C, 56·2; H, 7·0; N, 3·6%). It gave a very unstable hydrochloride (by evaporation from a cold aqueous solution), gradual decomp. from *ca.* 100°, complete decomp. with partial melting at *ca.* 148°, a nitrate (prepared similarly), gradual decomp. from *ca.* 110°, complete decomp. with partial melting at 143—145°, and a picrate (from aqueous solutions), decomp. from *ca.* 125° to 133—137°.

Ruwenine formed colourless plates, m. p. 175·5—179° (decomp. from *ca.* 164°), readily soluble in the usual organic solvents except ether, very slightly soluble in water [Found: C, 60·45, 60·75; H, 7·3, 7·5; N, 3·7, 4·0%; *M* (Rast; poor accuracy owing to instability), 371, 348, 360. $C_{18}H_{27}O_6N$ requires C, 61·3; H, 7·7; N, 4·0%; *M*, 353]. It gave a hydrochloride (by cold evaporation from aqueous solution and recrystallisation from absolute ethanol), decomp. at 222—224° with partial melting, a nitrate (prepared in a similar manner), decomp. from *ca.* 100° to *ca.* 140—160°, and a picrate (from ethanolic solution with aqueous picric acid; recrystn. from boiling ethanol), m. p. 186—188° (decomp. from *ca.* 160°).

Physiological effects. Retrorsine was used as standard in toxicological tests in which the hydrochlorides were injected subcutaneously, in small doses during some days, into 300—350-g. rats. Results are tabulated.

Alkaloid	Quantity (mg.)	Period (days)	Effects
Ruwenine .	2 × 25	1	Death after further 3 days. Early liver cirrhosis, periportal (unlike characteristic *Senecio* poisoning).
Retrorsine .	4 × 25	10	Death after further 2½ days. Liver damage acute and centrilobular.
Ruzorine .	2 × 25 1 × 50	10	No outward symptoms. Mild degenerative changes in the liver.

Acknowledgment is made to the Director of Veterinary Services, Kenya, for permission to publish this work.

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Kabete, Kenya.

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402. *Kinetics of the Association of Maleic Anhydride and Butadiene.*

By B. Eisler and A. Wassermann.

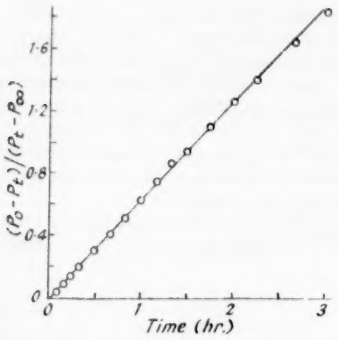
In previous papers (*J.*, 1936, 1028; 1939, 362, 381; 1950, 2205) the kinetics of Diels–Alder associations were reported for benzoquinone, tetrachlorobenzoquinone, 1 : 4-naphthaquinone, acraldehyde, 5 : 8 : 9 : 10-tetrahydro-5 : 8-*endo*methylene-1 : 4-naphthaquinone, and *cyclo*pentadiene as dienophiles. We have now measured the kinetics of the reaction of maleic anhydride with butadiene to give Δ^4-tetrahydro-*o*-phthalic anhydride. Second-order velocity coefficients, *k*, were determined by a vapour-pressure technique (Eisler and

Kinetics of maleic anhydride–butadiene reaction in benzene.

Temp.	Equimol. initial conc. of reactants (mole/l.)	*k* (l. mole^{-1} hr.$^{-1}$)	%, final conversion	Temp.	Equimol. initial conc. of reactants (mole/l.)	*k* (l. mole^{-1} hr.$^{-1}$)	%, final conversion
14·4°	0·833	0·0647 ± 0·007	62	25·0°	1·200	0·133 ± 0·005 ‡	58
14·4	0·903	0·0465 ± 0·011	69	25·0	2·000	0·137 ± 0·005	65
14·4	0·914	0·0534 ± 0·008	57	35·0	1·125	0·216 ± 0·010	39
25·0	0·311	0·106 ± 0·020	47	35·0	1·450	0·244 ± 0·010	54
25·0	0·601	0·117 ± 0·008	41	35·0	1·500	0·247 ± 0·010	54
25·0	0·980	0·128 ± 0·005 *	74	45·0	1·335	0·480 ± 0·020	64
25·0	1·200	0·138 ± 0·005	52	55·0	1·063	0·8175 ± 0·020	65

* Reaction mixture 0·5M with respect to triisoamylamine picrate.
‡ Reaction mixture saturated with maleic acid.

Wassermann, *J.*, 1953, 979), dry maleic anhydride and the same butadiene and solvent as in the previous work (*loc. cit.*) being used. The results of a typical experiment, and the values of k are given in the accompanying Figure and Table. The Arrhenius rate equation, $k = Ae^{-E/RT}$ is obeyed with $E_1 = 11{\cdot}7 \pm 0{\cdot}8$ kcals. and $\log_{10} A = 4{\cdot}2 \pm 0{\cdot}7$ (A in l. mole^{-1} sec.$^{-1}$). A previously investigated Diels–Alder reaction, involving benzoquinone and butadiene (Eisler and Wassermann, *loc. cit.*), is characterised by an activation energy $E_2 = 14{\cdot}6 \pm 0{\cdot}6$ kcals. The difference, $E_2 - E_1$ ($2{\cdot}9 \pm 1{\cdot}4$ kcals.) can be explained,



Maleic anhydride–butadiene reaction in benzene at 45·0°. Equivalent initial concentration of reactants, 1·335 mole/l. P_0, P_t, and P_∞ are the vapour pressures at zero time, time t, and after completion of reaction. The slope of the straight line gives $k = 0{\cdot}480 \pm 0{\cdot}020$ l. mole^{-1} hr.$^{-1}$.

inter al., by the influence of the C–O dipoles in maleic anhydride, which are liable to reinforce the dipole induction energy arising from the C=O groups (*J.*, 1935, 828, 1511).

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403. *The Polysaccharide of* Penicillium islandicum *Sopp.*

By J. BADDILEY, J. G. BUCHANAN, and E. M. THAIN.

DURING investigations on the colouring matters of *Penicillium islandicum* Sopp, Howard and Raistrick observed that addition of ferric chloride to the culture filtrate gave a heavy, amorphous precipitate with all six strains examined (*Biochem. J.*, 1949, **44**, 227). Although the nature of this material was not fully established it was thought to be a phosphorylated polysaccharide. Through the courtesy of Professor Raistrick we have re-examined this polysaccharide and the results of our studies are recorded here.

We confirmed that the material was insoluble in water but dissolved readily in dilute acids and alkalis, also that it reduced Fehling's solution only after acid hydrolysis at 100° (Howard and Raistrick, personal communication). Its solution in dilute hydrochloric acid gave a strong positive test for ferric ion (ferrocyanide), and phosphate determinations by the methods of Allen (*Biochem. J.*, 1940, **34**, 858) and Lowrey and Lopez (*J. Biol. Chem.*, 1946, **102**, 41) before and after acid hydrolysis indicated that the whole of the phosphate present (3·3%) was inorganic. It was concluded that the material was a mixture or complex of non-reducing carbohydrate and ferric phosphate. When a few drops of dilute aqueous ammonia were added to a suspension of this complex in water a rigid gel was produced. This was transformed into a relatively mobile solution on further addition of ammonia. It seems that the carbohydrate has a powerful solubilising effect on ferric phosphate.

After removal of ferric and phosphate ions by precipitation and ion-exchange methods, a solution of the carbohydrate was strongly acidic. This was a most unexpected observation on an eluate from a basic resin. The solution also passed unchanged through a column of the strongly basic Amberlite IRA–400 resin. A possible explanation of this phenomenon

is that the large molecules of an acidic polysaccharide are unable to penetrate the resin grains, thereby considerably reducing the acid-binding capacity of the column. The substance was recovered from solution by freeze-drying. Its ready and complete precipitation from aqueous solution by addition of alcohol was further evidence for its polymeric nature.

Acid hydrolysis of the polysaccharide liberated glucose, identified by paper chromatography in three solvent systems and by its characteristic pink colour in the carbazole reaction (Gurin and Hood, *J. Biol. Chem.*, 1939, **131**, 211). No other carbohydrate components were thus detected. Alkaline hydrolysis liberated a neutral polyglucoside and malonic acid, identified by paper chromatography and by isolation and comparison with an authentic sample. It appears then that the acidity of the polysaccharide arises from the presence of malonyl hemi-ester groups.

A 1 : 6-β-polyglucose bearing malonyl hemi-ester residues was isolated by Raistrick and Rintoul from *P. luteum* (*Phil. Trans., B.*, 1931, **220**, 255; Anderson, Howarth, Raistrick, and Stacey, *Biochem. J.*, 1939, **33**, 272) and was called luteic acid. In absence of a more complete investigation of the physical and chemical properties of the polysaccharide from *P. islandicum* it is not possible to assert its identity with luteic acid. However, certain marked similarities are indicated. After acid hydrolysis it gave a reducing value equivalent to 81—85 g. of glucose per 100 g. of polysaccharide, in fairly close agreement with the value for luteic acid (Raistrick and Rintoul, *loc. cit.*). Titration of the polysaccharide with sodium hydroxide indicated an equivalent of 575. Hydrolysis with excess of alkali liberated acidic groups equivalent to those present in the original polysaccharide. The amount of malonic acid set free by hydrolysis corresponded to 19·3 g. per 100 g. of the polysaccharide. These results agree approximately with a structure containing one malonyl hemi-ester per two glucose units, as is found in luteic acid.

Experimental

Purification of P. islandicum *Polysaccharide.*—The ferric phosphate-containing sample (400 mg.) was suspended in water (50 c.c.) and sufficient dilute aqueous ammonia added to produce a mobile solution. Hydrogen sulphide was passed in and iron sulphide removed by centrifugation. The precipitate was washed twice with water, and the combined solutions were passed through a column of IR-120 and then IR-4B resin. The acidic eluate was freeze-dried, yielding an almost colourless, porous solid (240 mg.), $[\alpha]_D^{23}$ −27°. To an aqueous solution of the polysaccharide was added ferric chloride, then dilute sodium hydroxide: a clear brown solution was obtained. Addition of Fehling's solution yielded a gel.

Hydrolysis.—(*a*) A sample (2 mg.) in 0·5N-hydrochloric acid (2 c.c.) was hydrolysed at 100° for 10 hr. Solvent was removed by evaporation in a desiccator, and the residue dissolved in a little water. Samples were examined by paper chromatography, using an aniline phthalate spray. A single spot corresponding to glucose was observed with the following solvent systems: phenol–water (R_F 0·37), butyl alcohol–acetic acid–water (R_F 0·31), collidine–water (R_F 0·38). The colour of the spot was the same as that given by glucose.

(*b*) The acidic polysaccharide (0·15 g.) was dissolved in 0·1N-sodium hydrogen carbonate (5 c.c.) and dialysed in a Cellophane sac against 0·1N-sodium hydrogen carbonate solution for 8 days at 4°. The sac contents were made 0·1N with respect to sodium hydroxide and left at room temperature for 18 hr. Alkali was removed by passing the solution through a column (20 × 1 cm.) of IR-120 resin, and acid in the eluate adsorbed on a column of IR-4B (OH^- form), from which it was eluted with 2N-ammonia (20 c.c.). The ammoniacal eluate was evaporated to dryness under reduced pressure, and a fraction of the residue run on a paper chromatogram in propanol–water–ammonia (6 : 3 : 1) and sprayed with Universal indicator which had been adjusted to pH 10 (Long, Quayle, and Stedman, *J.*, 1951, 2198). Only one spot was observed; this had R_F 0·24, which corresponded with malonic acid.

The residual ammonium salt was dissolved in water (0·5 c.c.), and silver nitrate solution added until no further precipitate was produced. The insoluble silver salt was collected by centrifugation, washed thrice with water, and decomposed with hydrogen sulphide. The silver sulphide was removed by centrifugation, the aqueous solution evaporated to dryness, and the residue sublimed (0·1 mm., bath-temp. 100°). The colourless sublimate, m. p. 130—132°, was undepressed in m. p. on admixture with an authentic specimen of malonic acid.

(*c*) The polysaccharide (14·5 mg.) was dissolved in hydrochloric acid (40 c.c., N) and heated at 100°. Samples were withdrawn periodically for determination of reducing value (Somogyi, *J. Biol. Chem.*, 1937, **117**, 771).

Time (hr.)	1	2	4	8
Reducing value (as g. of glucose liberated per 100 g. of polysaccharide)	66·3	81·2	81·2	85·1

Titration.—The acidic polysaccharide was further purified for titration by passing its aqueous solution through a column of Amberlite IR–4B (OH^- form) and one of Amberlite IR–120 (H^+ form). This effected almost complete removal of metallic and ammonium ions. The aqueous solution was freeze-dried as before. The polysaccharide (325 mg., dried at 110°/0·1 mm. for 1 hr.) required 10·59 c.c. of 0·0534N-sodium hydroxide for neutralisation to phenolphthalein. Treatment with excess of sodium hydroxide for 12 hr. at room temperature liberated acid groups equiv. to 11·28 c.c. of 0·0534N-sodium hydroxide.

The equiv. of the polysaccharide (from the first titre) is 575. 100 g. of the polysaccharide gave, on hydrolysis, 19·3 g. of malonic acid (from the second titre). Raistrick and Rintoul (*loc. cit.*) found that luteic acid had an equiv. of 434·7 and liberated 23·4 g. of malonic acid per 100 g. on hydrolysis.

Thanks are offered to Professor H. Raistrick, F.R.S., and Dr. B. H. Howard for generous gifts of the partly purified polysaccharide. We acknowledge financial support from the Department of Scientific and Industrial Research. This work was carried out during the tenure by one of us (E. M. T.) of an I.C.I. Fellowship.

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Autosynthesis.

FARADAY LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE ROYAL INSTITUTION, LONDON, ON MARCH 26TH, 1952.

By SIR CYRIL HINSHELWOOD.

SCIENCE, we believe, possesses an underlying unity. Faraday certainly seems to have been guided in his work by such a faith, and never ceased to search for connexions between apparently disparate natural forces, light and magnetism, magnetism and electricity, electricity and chemical affinity, and the insight with which he found them is part of the world's history.

I believe he would have wanted to find one between the intricate and beautiful kinetic mechanisms of chemistry and the mysterious self-reproductive power of living matter. He was indeed no materialist, but with his natural philosophic insight he would have seen that ultimate problems are unaffected by a successful translation of purely biological descriptions into the scientifically more fundamental language of physics and chemistry. In the translation the complex grammar of both languages must be borne in mind.

Genes and autosynthetic units

Biologists have long postulated fundamental self-reproducing units which they call genes, and they have for some purposes established what is rather like an atomic theory of these entities.

Organisms have been supposed to contain them, in a first approximation at least, fixed and unalterable, reproducing themselves, and transmissible by heredity. When cells of different types unite, the characters inherent in them are added and mixed. When cells divide there is a segregation, or division, of the character between the new-formed progeny. Many striking phenomena of heredity have been interpreted in terms of the resulting play of probabilities as the genes change their association like the coloured marbles in a mathematical exercise. The famous laws of Mendel revealed (in appropriately chosen examples) simple numerical ratios which could be interpreted in just this way.

As living cells fuse or divide, then, properties can be transmitted, gained, or lost, as though they resided in material entities possessed by some cells and not by others and subject to the laws of chance as discrete particles would be. For the biochemical properties of cells the principle of " one gene one enzyme " has been suggested.[1]

This whole conception, it is true, has its difficulties. To account for the ways in which even the simpler chemical functions of the cells of micro-organisms change in cultivation or on propagation, very complex sets of muliple genes have to be postulated, and they have to be assumed subject to the influence of what are called " modifiers " and " suppressors " to a degree which largely removes the simple numerical relations from which their existence was originally inferred.

Yet the power of living things to reproduce their kind, and the combinatory possibilities which are, in spite of all, quite manifest in their unions and divisions, have led most insistently to the idea of the self-replicating units of structure, and to the question of what special virtue resides in these strange entities.

There are, of course, in ordinary chemistry suggestive, though imperfect, parallels. In the growth of crystals, existing patterns guide the deposition of new material in ways which are remarkably precise, and new large crystals readily cleave to form numerous similar copies of an original small model. When attractive forces exist between units a copying process will generally give a structure of lower potential energy when the copy is exact, and this principle must surely play its part in autosynthesis. But this is not enough. The analogy of moulds and templates and the corresponding casts, and of positive and negative replicas, has often been invoked. It carries the same principle a stage further, but still seems to provide only a possible element in the solution of the problem, rather than the solution itself.

In the polycondensation reactions so much studied by chemists in recent years there is a continuous growth of substance, often not altogether unlike living matter in molecular structure, and there is even replication in so far as the well-known kinetic mechanism of the

[1] Cf. Monod, Biochemical Society Symposia, No. 4, 1951, p. 51.

" chain transfer " process cuts up what is formed into separate units. But this too can be but one element in the solution of the problem.

The obtaining of certain viruses in the form of crystals certainly illustrates the relevance of these various analogies, but it illustrates also their incompleteness, for viruses cannot reproduce themselves in isolation, and need to invade other living cells. Their own nucleoprotein substance increases not at the expense of the infected cell, but of medium constituents,[2] so that it is the machinery of the cell which they can use, not its material upon which they necessarily prey.

This in a general way is really the key to the whole problem. Just as the virus is not a self-duplicating unit in its own right, so there is probably no other single substance or unit which possesses this property. Viruses have been likened to genes and this parallel in turn has been challenged. But they may well have this in common that neither is the elusive autosynthetic unit, which indeed may well have no more independent existence than the philosopher's stone or the elixir of life.

The substances of which living cells are built are complex and thermodynamically unstable. They are not formed spontaneously under ordinary conditions, and a laboratory synthesis would demand a long series of very elaborately arranged experiments with numerous intermediates first separated and then brought together again in appropriate combinations. Great reductions in entropy have to be compensated.

Such compensation in itself is easily possible if the reactions of negative entropy change are linked with others of positive change, such as oxidations, and this linking commonly occurs by the intervention of common active intermediates in the coupled system.

Another source of compensation is illustrated in crystal growth itself. Here an ordered structure is produced from a disordered group of molecules and so entropy decreases. But energy is released and must be conducted away to raise the temperature and entropy of something else, and thus the balance is preserved. For the ordered structure to arise, however, a model must be there to copy, or else the initiation of the process may be long, or in complicated cases, almost indefinitely delayed. Copying is far easier than invention.

In the reproduction of a cell there is indeed copying, but degradation of energy also occurs, and highly complex series of reactions combine, as it were symphonically, to give among the total products certain substances of very low entropy. It is the interplay of all these processes which must make autosynthesis possible, not the replication of individual genes as such.

The guiding of synthesis by existing structures is indeed necessary, and these existing structures are in general so complex as to be nearly incapable of spontaneous appearance. Living matter is thus largely the slave of heredity.

But the two aspects of the gene, that, namely, which is responsible for the fundamental character of a cell on the one hand, and the self-reproducing unit on the other, must be regarded separately. The types may be permanent but the elaborate and subtle interplay between them is a matter of organization and balance, and these are things which unlike the basic entities themselves are labile.

The interplay presents kinetic problems of great interest, and the biological analogies which the results indicate, and which will be briefly mentioned, are highly suggestive. They are certainly of significance though in just what ways is perhaps hardly yet agreed. In the meantime we may at least say that we are studying a new type of chemical reaction system.

Mutually dependent reaction systems

Some fundamental principles are illustrated by a very simple system of kinetic equations. Suppose there are two substances each of which is itself being formed at a rate determined by the catalytic action of the other so that

$$dX/dt = \alpha Y \text{ and } dY/dt = \beta X$$

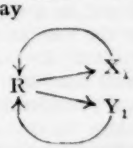
Neither X nor Y in isolation could increase in an autocatalytic manner, yet these two equations show that after a period of rather complex adjustment the amounts are given by

$$X = X_0 e^{kt} \text{ and } Y = Y_0 e^{kt}$$

X_0 and Y_0 being the values at time $t = 0$. The steady state reached by the system after a long time is described then by the equations $dX/dt = kX$ and $dY/dt = kY$, each constituent being apparently self-duplicating. The result is similar when any number of constituents are formed in such a way that the increase of each depends upon the catalytic action of the others.

[2] Cf. Andrewes, *Proc. Roy. Soc.*, 1952, *B*, **139**, 313.

If we have the set of equations $dX_1/dt = \alpha X_2$, $dX_2/dt = \beta X_3$, $dX_3/dt = \gamma X_4$, $dX_4/dt = \delta X_5$ . . . . it can be shown that in the steady state which is finally reached $dX_1/dt = kX_1$ $dX_2/dt = kX_2$, and so on. Nor does this apply only to a single linear sequence. Suppose we have a system coupled in the following way



where R forms X_1 or Y_1 from different substrates in a complex system, X_1 and Y_1 being, as it were, modifications of similar enzymes, but each guiding the further formation of R. We should then have the equations $dX_1/dt = \alpha R$, $dY_1/dt = aR$, $dR/dt = \beta X_1 + bY_1$.

The solutions, even with this very simple cycle, look rather complicated : they are

$$R = \tfrac{1}{2}\left\{R_0 + \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}e^{kt} + \tfrac{1}{2}\left\{R_0 - \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}e^{-kt}$$

$$X_1 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} =$$

$$\tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} + \frac{\alpha R_0}{k}\right\}e^{kt} + \tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} - \frac{\alpha R_0}{k}\right\}e^{-kt}$$

$$Y_1 = \frac{a}{\alpha}\{X_1 - (X_1)_0\} + (Y_1)_0$$

where $k^2 = \alpha\beta + ab$.

As soon as t is great enough, however, the following ratios are established since the terms in e^{-kt} vanish,

$$X_1/R = \alpha/k = \alpha/(\alpha\beta + ab)^{\frac{1}{2}}$$

and $$Y_1/R = a/k$$

If now a small sample of matter in which these proportions are established is transferred to a fresh environment of similar character $(X_1)_0$, $(Y_1)_0$ and R_0 are in these ratios, and, from $t = 0$, the above equations reduce to the form

$$R = \tfrac{1}{2}\left\{R_0 + \frac{\alpha\beta R_0 + abR_0}{k^2}\right\}e^{kt} + \tfrac{1}{2}\left\{R_0 - \frac{\alpha\beta R_0 + abR_0}{k^2}\right\}e^{-kt}$$

$$= R_0 e^{kt}$$

and similarly $X_1 = (X_1)_0 e^{kt}$ and $Y_1 = (Y_1)_0 e^{kt}$.

The system

$$Y_2 \longleftarrow Y_1 \longleftarrow R \longrightarrow X_1 \longrightarrow X_2$$

yields still more complex relations for the non-steady state. The formation of X_2 may on occasion lag behind that of Y_2, or *vice versa*, and extraordinary fluctuations in the relative amounts of the components may occur. These phenomena of the non-steady state, as we shall see, may be of great importance. But eventually the simple exponential law of increase is followed by everything.

Thus neither the length of the chain of mutually dependent processes, nor a bifurcation in the sequence, affects the establishment of what appears as an autosynthesis. It may therefore reasonably be concluded that a large variety of quite complexly interlocking patterns of reactions will be subject to the same principle.

It sems not unlikely, then, that there are after all no individual units endowed with mysterious powers, but that the mystery, indeed the miracle, lies in the initial conjunction of partial systems which minister to one another's needs in the appropriate way. What sorts of system would perform such functions? Catalytic degradations and syntheses are of course performed by enzymes which are largely protein. Cellular nuclei, which are the seat of special activity, contain nucleic acids; viruses themselves are largely nucleoprotein in nature.

The nearest thing to a system autosynthetic in its own right—though it is of course not really so—is a virus, and the nucleoprotein character of viruses has often suggested the great importance of protein–nucleic acid interactions. There is indeed experimental evidence for such

a relation in the patterns of mutually dependent reactions which have just been referred to. Malmgren and Heden [3] found that the nucleic acid content of bacteria at various stages of their growth cycle was correlated with the rate of growth at that stage. The amount of ribose nucleic acid in *Bact. lactis aerogenes* cultured in a wide range of different conditions has been found, moreover, nearly proportional to the rate at which the cells have grown.[4] This last relation follows from the equations $d[\text{Protein}]/dt = \alpha[\text{Nucleic acid}]$ and $d[\text{Nucleic acid}]/dt = \beta[\text{Protein}]$, with α a more or less universal constant. This result supports the idea which is already suggested by Astbury's structural considerations that in the synthesis of protein the nucleic acid guides the order and determines the rate of accretion of the amino-acids, and that conversely the protein is, as it were, the heterogeneous catalyst by which the nucleotide units are built together. Characteristic relations of " polypeptide chains and nucleotide columns " have existed from the beginning, as Astbury says " along a line of molecular heredity which may not be broken except at the cost of starting at the beginning again."

Kinetic principles of cell growth

If, then, the autosynthetic function is not inherent in any one cell component, but emerges from the harmonious co-operation of many, it is obvious not only that the growth of the cell and the reproduction of its matter are very intimately linked with the working of the enzymes, but that the reproduction of these enzymes is intimately linked with their own working, since it is this which in turn enables others to work and provide the synthetic material for them. As we have seen, the complex equations of the interlocking reactions are in many respects equivalent to another set $dX/dt = kX$, $dY/dt = kY$, and so on, so that we have a rational basis for a formulation which in effect runs :

enzyme + metabolite 1 = more enzyme + metabolite 2

This I shall call the *first kinetic principle*.

It is a simple mathematical consequence of this that on continued growth the proportions of the various kinds of material present in a system will settle down to stable values. If, moreover, conditions of growth change in such a way as to alter the velocity constants, these proportions will change also. This we might call the *second kinetic principle*.

We must next bear in mind that living matter is organized in cells, and that these from time to time divide so as to maintain a roughly constant size. The detailed mechanism of cell division need not be discussed. It must, however, come about as a result of the area/volume changes accompanying increase in size. These lead to changed internal concentration of metabolites and products. What is important for the present purpose is the simple and natural hypothesis that at the moment of division some important cell component or set of components plays the rôle of a key substance, and that the process is initiated as soon as the amount of this substance reaches a more or less constant critical limit. This will be the *third kinetic principle*.

It is not without direct experimental support. Various observers [5] showed that in certain animal cells the amount of deoxyribose nucleic acid was nearly constant. Caldwell and Hinshelwood [6] found that cells of *Bact. lactis aerogenes* grown under a wide variety of conditions, which gave variable growth rates and widely variable total nitrogen contents, had nevertheless nearly standard contents of deoxyribose nucleic acid. There is no need to suggest a definite identification of deoxyribose nucleic acid with the division-controlling substance or system, but the principle that the amounts of one or more key constituents may be taken as invariants seems to be quite well founded.

From these three kinetic principles there follows a *fourth*, verifiable by mathematical calculations with simple models, namely, that in the kind of systems which have been described those proportions of constituents will finally be established which lead to a maximum rate of growth in the actual environment.

This indeed is something like a process of natural selection. If in a population of cells some individuals could reproduce themselves faster than others then they would outgrow and supplant them. But in a similar way a quantitative scheme of reactions, even one not already established in any cell, will gradually replace other quantitative schemes which offer smaller resultant reaction rates.

[3] *Acta Path. Microbiol. Scand.*, 1947, **24**, 448.
[4] Caldwell and Hinshelwood, *J.*, 1950, 3156.
[5] Boivin, Vendrely, and Vendrely, *Compt. rend.*, 1948, **226**, 1061; Mirsky and Ris, *Nature*, 1949, **163**, 666. [6] *J.*, 1950, 1415.

Not only would the proportion of enzymic and other material in a cell change in this sense, but what may be termed the " reaction pattern " of the cell as a whole could be superseded by another and more effective one. Cells possess vast numbers of enzymic functions, and many orders and combinations of simple unit processes can be combined to give the final syntheses. If these processes are used in one order and at a given rate, there will be definite ratios of the various material components set up; if in another order and at another rate, different ratios. In the end the available reactions will be used according to that pattern which gives an optimum rate, and the cell composition will correspond.

Simple illustration of an automatic adjustment in a cell containing effectively autosynthetic systems

Suppose an enzyme system I produces a diffusible substance which is used by a second enzyme system II. Let the total amounts of I and II at any time be X_1 and X_2 respectively, contained in n cells. Let the concentration of the intermediate be c. In any cell this will very rapidly reach a steady value determined by the equation

$$dc/dt = A(X_1/n) - B(X_2/n)c - Cc = 0$$

where A, B, and C are constants. The first term of this expression represents formation by I, the second consumption by II, and the third loss by any other means. If II is the component upon the formation of which cell division must wait, then $n = \beta X_2$ where β is a constant. Thus $c = \alpha X_1/X_2$, where α is another constant.

The rates of increase of I and II are given by

$$dX_1/dt = kX_1$$
$$dX_2/dt = k_2X_2c = k_2\alpha X_1$$

Let the ratio $X_1/X_2 = v$

$$\frac{dv}{dt} = \frac{X_2\frac{dX_1}{dt} - X_1\frac{dX_2}{dt}}{X_2^2} = k\frac{X_1}{X_2} - k_2\alpha\frac{X_1^2}{X_2^2}$$
$$= v(k - k_2\alpha v)$$

If $k_2\alpha v < k$ when $t = 0$, dv/dt is positive. Thus v increases with time. Presently, however, v reaches such a value that $dv/dt = 0$, whereupon no further change occurs, since there is no increase in v to alter the value of the differential coefficient. The ratio of X_1/X_2 is now stable and $k_2\alpha v = k$.

Suppose now some agency disturbs the concentration c and so interferes with cell growth. (It could be a toxic substance or a foreign enzyme which destroyed the diffusible metabolite, but this need not be specified.) Since $dn/dt = \beta dX_2/dt$, and dX_2/dt depends upon c, the growth rate is lowered. α assumes the smaller value α'. dv/dt, which was zero, now becomes positive. v now increases until $k - k_2\alpha' v$ is once more zero, whereupon there is a new steady state. $(1/n)dn/dt$, which had fallen below k, has now risen to equal k once more.

This single example illustrates the principle of automatic adjustment.

Biological analogies of systems showing automatic adjustments

So far the theme has been that autosynthesis involves a dove-tailing of mutual supply systems, and that these should possess the property of self-adjustment to show maximum growth rate, whereupon they reach a steady state, in an environment which contributes the proper raw materials. The biological analogies of this picture are obvious. Unicellular organisms show continued logarithmic growth ($X = X_0e^{kt}$) in suitable constant environments. In new environments long periods of adjustment or lag phases may be necessary before the steady state is established. In this state the simple law of autocatalytic growth is closely followed, the amount of material increasing in geometrical progression with time. On transfer from one environment to another they show adaptive responses, initially slow or nearly negligible rates of growth gradually rising to an optimum. The equations which have already been shown predict just such complicated lag phases.

These adaptive responses include the development of the power to use with maximum efficiency unfamiliar sources of nitrogen or carbon, or to grow with unimpaired speed in the presence of toxic agents which initially are inhibitory. It is an interesting hypothesis that during the lag phases and periods of adaptive response a given reaction pattern is establishing itself, sometimes in competition with another. Here we are presented with systems which are

of the greatest interest not only in biology, where the phenomena shown by adapting cells are of great fascination, but also in chemical kinetics.

Until recently there has been reluctance of many biologists to admit even in principle the possible interpretation of such phenomena in terms of kinetic mechanisms, and they have believed most of the apparent adjustments to depend upon natural selection of spontaneously occurring mutant cells. But more recently there seems to be an increasing willingness to admit the possibility of both mechanisms. And in particular cases there is indeed very strong evidence for the occurrence of just the sort of automatic adjustments which have been described.

Reversibility of adjustments

The whole state of affairs suggested by the foregoing considerations is very different from that where biochemical properties reside in self-replicating genes which are unchangeable save by a catastrophic event of some kind (usually called a mutation).

The results of experiments on automatic adjustments in cells suggest rather an interlinked system of mutually dependent parts, no one of which could grow in isolation. There is, according to this view, no autosynthetic type of structure as such, and the permanence of genes (and the essential dependence of really fundamental cell properties upon them) simply reflects the stability of many chemical compounds and the fact that complex structures of low entropy are in any case extremely unlikely to arise *de novo*. Any characteristic piece of cell texture would thus constitute a gene in the sense that it might determine a property on the one hand, and on the other hand be continuously resynthesised in the co-ordinated interplay of cell processes.

We have thus two major factors: fundamental key structures, and their quantitative kinetic relations to one another. Both are of importance in the building of cells with given qualitative and quantitative properties. Fundamental key structures are likely to be relatively permanent, quantitative relations to be highly variable.

An important question therefore is how far changes in properties shown by cells in new circumstances persist in the progeny when the same circumstances no longer prevail. Not infrequently they do seem to persist. Once a bacterium, for example, has learnt how to use a new sugar for growth, it often behaves as though it remembered how to do this even in the absence of the sugar itself. Inheritable properties of this kind might indeed seem to indicate discontinuous and irreversible structural changes.

But the story is not quite so simple. To begin with, it is quite a question what is meant by heredity in a unicellular organism which increases in size and then splits in two. Changed chemical organization of the so-called parent cell is inevitably preserved to some extent in the two cells formed by binary fission, and the problem of how many generations inherit the new property may be no more than that of how long a new organization imposed on a mass of autosynthetic material requires before it can give place to another.

The establishment in a fresh environment of a new reaction pattern accompanied by different proportions of the cell components should, according to the kinetic propositions already set out, be reversible on return to the original environment. But there are various chemical reasons why the rate of reversion may be slow, or even very slow indeed. One of the most important is the lag which may theoretically be expected to attend the establishment of a new reaction pattern. If growth by an alternative route is proceeding actively during this lag the new pattern may never have a chance to develop.

According to this conception the problem is not so much one of stability of adapted forms as of rate of reversion. And in fact the biological systems to which these analogies may apply do show varying and highly complex time relations in their adjustments.

For example, if bacteria are adapted to a new medium, they may lose their adaptation at a whole series of different rates according to the length of time for which they have, as it is said, been trained. But an eventual return to the original state seems to be the commonest fate (unless in the meantime other factors have intervened), so that the argument from heredity can by itself not abolish belief in the kind of kinetic adjustments to which reference has been made in the foregoing.

Whether or not I am right in what I have said about heredity and about permanence, the fact remains that, on general thermodynamic and kinetic grounds, cells must be systems possessing something at least of the character I have described, and that the equations of such systems predict adjustments as they modulate from one growth regime to another. If the phenomena which look like adaptive adjustments are really something else, then I feel sure that true adaptive responses will still be found in the end to have been going on in secret.

Most of these adjustments are of course limited in range, and so do not in any way weaken belief in a fundamental substratum of substance with which given qualitative characters are necessarily linked. The relation of the adjustable to the permanent elements in cell organisation is indeed one of the major questions, and more will be said of it shortly. But there is first a little more to say about the reaction pattern itself. It is after all even more significant than the key structures in indicating the nature of the kinetic laws by which the cell establishes and maintains its organization.

Multiple reaction patterns

The multiplicity of the reaction networks has already been mentioned. They may branch, and alternative sections may operate simultaneously and in competition, in phase with one another, or with one lagging while the other functions. To them correspond a whole series of enzymic organizations of the cell, which represent various possible states of adaptation to various environments.

This conception helps in the understanding of a whole range of remarkable phenomena observed with micro-organisms such as bacteria and yeasts.

Sometimes, to quote one example, a bacterium on transfer from compound A as a carbon source to compound B, attains its optimum growth in B without any impairment of its growth in A. Sometimes on the other hand, growth in A is impaired and the adaptation to the two sources at once seems impossible. What seems to happen is that the cells can grow in B by two alternative reaction patterns, one compatible with that required for growth in A and one not. Sometimes the one of the alternatives lags in its establishment and then the behaviour appears different from what it is when this alternative is mobilized. In the light of kinetic principles such phenomena become generally intelligible.

The great part played by the combination of reaction routes is illustrated by an example taken from the yeasts. These are a little more complex than bacteria and in particular two cells of haploid yeasts may fuse together to give one of more elaborate structure, a diploid. From diploids, haploids may be re-generated in the process of sporulation. Now when two haploids of a certain strain united to give a diploid, its growth rate in the sugar raffinose was found, after a considerable period of adaptation, to be greater than that of either of the original haploids. In other words, the potentially more complex reaction pattern could achieve a greater overall efficiency. But before the adaptation the diploid initially showed a much greater lag in utilizing the sugar than either of the haploids. Although it possessed all the potentialities for more rapid growth, the disturbance of organization on cell union did actual harm, and the more elaborate pattern of the reactions used by the diploid required longer to establish.[7]

Organization and substratum

However, it must not be forgotten that the gene of the biologist is sometimes an entity which passes from parent to offspring according to the play of probability. What is the physico-chemical basis of Mendelian heredity?

May we pause a moment to remember Faraday once more? His laws of electrolysis provided the main support of dualistic chemistry, and yet his discovery of benzene opened a field of investigation where, as strikingly as in any, there has been revealed the subtle ways in which polar and non-polar influences combine to determine the behaviour of chemical substances. His liquefaction of chlorine, and his work on heterogeneous catalysis paved the way for the understanding of the multitudinous modes of interaction of matter and the elaborate hierarchy of chemical forms. It is the complexity of this hierarchy which must now be invoked.

To behave as a Mendelian gene an element of cell structure must be transferable as a single unit in processes such as division. It must therefore be localized and possess a certain degree of mechanical independence. It could therefore be a single unit of macromolecular structure of definite chemical composition, or else an association of units constituting a separable phase in the physical sense.

Not only are chemical molecules themselves of widely varying stability, but their modes of interaction with others of the system in which they exist is also graded over a wide range. They form aggregates which enter into all the complex relations of phase equilibria and of colloid chemical phenomena. Macromolecules have their own laws of regimentation and they form sheets and chains folded in elaborate ways which react in turn on their relations to their neighbours. In macromolecular chemistry the ordinary differences between molecules and

[7] Kilkenny and Hinshelwood, *Proc. Roy. Soc.*, 1952, *B*, **140**, 352.

masses, surface and bulk phases, homogeneous and heterogeneous systems lose much of their definiteness. In such a world mechanical and chemical separability must show wide variations. If some key molecular unit or combination of units is mechanically separable from the rest without too drastic an upset, then it can be gained and lost as a whole when cells unite or divide. We then have the condition that some entity is recognizable as a Mendelian gene.

But even so the complete manifestation of its properties, and still more the provision of material for its synthesis, depends upon its quantitative relation to other structures, and upon the proportions of other constituents in immediate reaction with it, and with other key structures And all these are subject to the subtler changes envisaged in theories of adaptive response.

Yeast cells provide an illuminating example of this thesis. Diploid yeasts sometimes divide to give four haploid spores from which haploid sub-strains can be cultivated. In certain examples the diploid will utilize the sugar galactose for growth, while of the four derived strains two will do the same while two (to all intents and purposes) will not. Evidently two key structures responsible for galactose metabolism have divided themselves bodily between four spores, so that two of these spores are fortunate and two are not. Yet even the two positive spore cultures show the clearest adaptive phenomena, and develop their optimum power of growth in galactose only after long periods of adjustment which there is every reason to believe may involve changes in reaction pattern of the kind already discussed.[8]

Nor is this all; even the negatives, if left with galactose for perhaps ten or twenty times as long as the positives require even in the unadapted state, eventually develop yet another reaction route by which they succeed in growing with utilization of the sugar.

The complete gain or loss of a key structure seems, then, to be something of a limiting case. Organizational changes with a kinetic basis are ever-present. What intermediate degrees of change can be envisaged?

Apparently discontinuous changes in cell properties are often called forth by exposure to ultra-violet light or other "mutagenic agents." One can well understand that some key structure may become completely extirpated by that treatment, and indeed in most known cases the change occurring is the loss rather than the gain of a character—a deficiency in the metabolic machinery usually results. The deficiency may be slowly repaired if the cells are cultured for long enough in conditions conducive to adaptation. The question then arises whether a second, spontaneous, mutation reversing the effect of the first has occurred, or whether the key structure, not having been wholly eliminated, is gradually repaired by a quantitative adaptive adjustment.

Since the effect of ultra-violet light varies continuously and quantitatively, and since the rather uneventful process of subculture recreates a lost character while the more potent agency of the ultra-violet light is unable to do so (and causes little save damage), the quantitative interpretation of these phenomena has perhaps something to be said for it.

But there are obvious kinds of qualitative change which should in appropriate circumstances be imposable without an excessively drastic upheaval in the cell economy, and it would be surprising if these did not play their part, the range of chemical forms and textures being so wide and capable of such subtle gradations. Two of the most important kinds are, on the one hand, the sequence and arrangement of peptides in proteins or of nucleotides in nucleic acids, and, on the other hand, the different configurations into which protein chains can fold themselves.

Cohn has found that during the induced formation of β-galactosidase in *E. coli* there is indeed production of a substance with given antigenic properties in place of another with different though related properties.[9] This may of course represent simply the quantitative shift in proportions of two substances both present all the time (though perhaps in minute amount), but it may very well indicate an imposed qualitative modification in the proteins.

If nucleic acid and protein synthesis are indeed mutually guided, it seems not unlikely that a given nucleic acid may guide the formation not of a single protein only but of several related ones. These proteins may then react enzymically each with the appropriate member of a not too diverse series of substrates. If this is so, then during an adaptation to optimum growth in a new medium there may be minor qualitative changes in proteins as well as major quantitative changes in the proportions of the various cell constituents.[10]

[8] Winge and Laustsen, *Compt. rend., Trav. Lab. Carlsberg*, 1937, **22**, 235; Kilkenny and Hinshelwood, *Proc. Roy. Soc.*, 1951, *B*, **139**, 73.
[9] See Monod, Cohen-Bazire, and Cohn, *Biochim. Biophys. Acta*, 1951, **7**, 585.
[10] Cf. *J.*, 1952, 745.

Pauling has discussed the formation of antibodies in terms of protein folding. When a so-called antigen is introduced into blood serum, it induces the formation of an antibody which for a considerable time retains the property of precipitating antigen. According to Pauling, antigens and antibodies have complementary structures in portions of their molecules, and in fact in at least two regions. As a result, the formation of a composite framework, constituting the precipitate, becomes possible. He suggested that the antibody differs from the normal serum only in the way in which certain regions of the globulin polypeptide chains are folded, and he pointed out that there will be many configurations of nearly equal energy, so that many specific antibodies can be induced by different antigens.

The folding of parts of the chain to conform to the shape or force field of another molecule is an example of what is often called " template " action. Some authors have postulated such a relation of mould or matrix to the corresponding casting for the building of genes from their precursors, and indeed have assumed a symmetrical relation for the alternating formation of both. Many variants of such ideas occur, and the Mendelian genes have not been the only entities assumed to be duplicated in this way. Thus Spiegelman at one time envisaged cases where certain enzymes were " capable of self-duplication without the necessity of genic intervention," the sole function of the gene itself being " the initiation of the enzyme synthesis."

It is clear from all this that, even within the framework of essentially constant basal chemical types, not only may quantitative proportions vary but subtler kinds of qualitative modification may occur, sometimes of what we should once have called a colloid chemical nature, and sometimes involving minor shifts in chemical composition. The precise rôle of all the possible kinds of modification is still to be explored and offers a fascinating field of study.

The decline of the cell economy

The theme of the complex interlocked reaction pattern of the cell with its hierarchy of physical and chemical forms in their varying degrees of interdependence has naturally been most in evidence in connexion with synthesis, growth, and adaptive changes. It dominates also the picture of the process by which cells suffer decline and death. The physical chemistry of this is of outstanding interest.

When a large population of bacterial cells is kept in an environment unfavourable to growth the cells gradually die. If the logarithm of the number of survivors is plotted against the time, the curve obtained varies in form, but sometimes approximates to a straight line (as would be shown accurately by the single-stage decay of a radioactive element). The straight-line relation, if absolute, would imply that the probability of death for an individual cell is independent of its previous history. Rather naive interpretations of this conclusion have occasioned much controversy. Death of the cell has been attributed to an accidental encounter between a quantum of radiation or the molecule of a toxic substance, on the one hand, and a highly localized vulnerable centre on the other. The " bullet " theories have been opposed by another group which ascribe death to a progresive deterioration, give to each cell a definite survival time, and rightly emphasize that this time will not be uniform but will show a statistical distribution in the population in accordance with the inherent variability of all biological systems.

The difficulty about such theories is that the statistical distribution which they must assume to account for a logarithmic decline is one which seems inherently improbable and has no independent support: it is, namely, that the largest proportion of the cells possess the minimum resistance rather than one nearer to the average value.

The matter assumes, however, a more natural aspect when looked at in relation to the complex reaction pattern of the cell. In many different ways synthesis and destruction are in continual opposition. Enzymic reactions are reversible. Cell material is labile and breaks down when not continuously built up. Even when a cell is in a state of apparent quiescence, as judged by the criteria of growth and division, it remains the seat of lively metabolic exchanges. Living cells multiply, dead cells suffer lysis, but synthesis and degradation in general are known from the evidence of radioactive tracers to occur far more rapidly than either observable growth or observable decay. The immense network of reaction patterns when no longer working with the complete co-ordination necessary for effective autosynthesis is still capable of constructive functions, and partially disorganized but still not purely destructive activity continues.

When some parts of the cell material break down they yield diffusible compounds which can be incorporated into other parts by the operation of the still effective partial mechanisms. It

can easily be shown that there may result an actual waxing and waning of different enzymic functions. When a number of these undergo quasi-periodic variations bearing no regular phase relation to one another, it becomes, for any individual cell, a matter of chance when the functions happen to pass through, say, their minimum values together. (This, of course, is the essential theoretical basis of the law of radioactive decay.)

We can now form the following picture of cell decline. A certain general decay of all the functions sets in, and until this has reached a certain stage, the chance of death is small. This represents an initial stage of slow progressive decline and corresponds to the period of delay which is sometimes observed to precede the onset of the approximately logarithmic phase. Next comes the phase during which death ensues when various quasi-periodic fluctuations reach unfavourable minima together. The reduction of the living population now follows roughly the exponential decay law. This law may be more or less satisfied to the end, but sometimes an effective degree of adaptation may be achieved. If so, there is a final phase in which a certain proportion of survivors exhibit exceptional longevity. This broad conception of the process covers most of the experimentally observed facts. The general form of the logarithmic survival curve is in fact sigmoid rather than linear except in its central portion.

Conclusion

The physical chemistry of highly co-ordinated reaction systems is in its infancy both theoretically and practically. All I hope to have shown is the cogency and relevance of its problems. There is scope for powerful mathematics in the proper working out of the general conditions for the existence and functioning of such systems, and for every resource of ingenuity and technique in the practical exploration of these problems.

The biological aspects of the question are equally alluring, and, to mention only one, the decision as to which changes occur by modification of individual cells and which by shifts in population balance gives rise to arguments with surprising depths of subtlety. I have not attempted to deal with this here, partly because time is insufficient, but also because I should like the purely chemical aspect to appear in its own right.

It may seem a long way from here to Faraday, but in several respects, as I have indicated in passing, the story is a continuous one, and I do not think he would have deprecated the study of cell function in the light of physico-chemical ideas.

The last words shall be with Faraday himself. Whoever may prove less right in some of the more controversial issues of the moment may perhaps ponder what he says in the Preface to Volume I of *Experimental Researches in Electricity*: "Although I cannot honestly say that I *wish* to be found in error, yet I do fervently hope that the progress of science in the hands of the many zealous present cultivators will be such as, by giving us new and other developments, and laws more and more general in their applications, will make even me think that what is written and illustrated in these experimental researches, belongs to the by-gone parts of science." And to those who doubt the wisdom or expediency of such enquiries, may be quoted the words he used in a letter to Tyndall (June 28th, 1854): "But then our subjects are so glorious, that to work at them rejoices and encourages the feeblest; delights and enchants the strongest."

ONE HUNDRED AND TWELFTH ANNUAL GENERAL MEETING, THE REPORT OF COUNCIL, AND ACCOUNTS FOR THE YEAR ENDED DECEMBER 31st, 1952

ONE HUNDRED AND TWELFTH ANNUAL GENERAL MEETING.

THE One Hundred and Twelfth Annual General Meeting of the Chemical Society was held in Burlington House at 10.30 a.m. on Friday, March 27th, 1953. The President, Professor C. K. Ingold, was in the Chair.

Professor E. D. Hughes, Honorary Secretary, read the notice convening the meeting.

The President then called upon Professor H. Burton, Senior Honorary Secretary, to present the Report of Council for 1952. Professor Burton stated that the year had seen a further increase in the Fellowship of the Society, which now numbered over 9,000. He referred to the honours which had been awarded to Fellows of the Society during the year, and mentioned particularly the award to the President of a Royal Medal announced by the Royal Society.

The *Journal* had continued to increase in size, but the number of papers received had declined during the past few months, and this indicated that possibly the period of expansion had come to an end. The Council was much indebted to the many fellows who had acted as referees of papers. In conclusion, Professor Burton expressed the Council's appreciation of the work undertaken on behalf of the Society by its Local Representatives and paid a tribute to the Society's permanent staff.

In presenting the Accounts for 1952, the Treasurer drew attention to the uncertainty regarding the future of *Abstracts* and to the contingent liability which appeared as a footnote to the balance sheet. He gave an account of the negotiations which had taken place in an attempt to secure financial assistance to enable publication of *British Abstracts* to continue in 1953. If support was forthcoming it was hoped that more permanent arrangements could be made for subsequent years. The Government had already made an interim payment of £5,000 to enable the abstracting organisation to be kept in being and had agreed to make a further substantial payment on the understanding that the balance of the total amount required would be forthcoming from Industry. The appeal to Industry had recently been issued, but it was too early to gauge the result.

In reply to a Fellow who mentioned the crowded accommodation at certain of the Society's meetings, it was stated that attendances were very difficult to estimate in advance. Meetings held in the Society's own rooms had often been overcrowded, but there had also been occasions when the attendance at meetings in other lecture theatres had been disappointingly small.

After discussion the Report of Council and the Accounts for 1952 were unanimously adopted on the proposal of Professor D. H. Hey, seconded by Dr. T. S. Stevens.

The President announced that the following Fellows had been elected to fill vacancies on the Council :

Vice-President :

Professor R. D. Haworth.

Elected Ordinary Members of Council :

Constituency I :

Professor F. Bergel.
Professor M. J. S. Dewar.
Dr. A. I. Vogel.

Constituency IV :

Dr. I. J. Faulkner.
Professor Brynmor Jones.

On the motion of the Treasurer, seconded by Dr. L. E. Sutton, Messrs. W. B. Keen and Company, Finsbury Circus House, Blomfield Street, London, E.C.2, were re-appointed as the Society's Auditors for 1953.

In conclusion, a vote of thanks to the President, Officers, and Council for their services during the past year was proposed by Professor Brynmor Jones and carried with acclamation.

After an interval the meeting was resumed at 11.30 a.m. The President referred to the award to Dr. F. Sanger of the Corday–Morgan Medal and Prize for 1951 in recognition of his contributions to experimental chemistry published in two papers on " The Amino-acid Sequence in the Phenylalanyl Chain of Insulin." Dr. Sanger was prevented through illness from attending in person to receive the award.

The President then delivered his Presidential Address, " Old and New Ideas on Saturated Re-arrangements." At the conclusion of the Address a vote of thanks to the President, proposed by Sir John Simonsen, was carried with enthusiasm.

REPORT OF COUNCIL FOR 1952.

I. ROYAL PATRONAGE.

Through the sudden death of His Majesty King George VI, the Society mourned the loss of its Patron. An address of condolence, and of loyalty on her accession, was conveyed to Her Majesty Queen Elizabeth II. A respectful message of sympathy was also sent by the Council to H.M. Queen Elizabeth, the Queen Mother.

The Council was pleased to announce, in June 1952, that Queen Elizabeth II had continued the tradition established by her father and had graciously extended her Patronage to the Society.

II. FELLOWSHIP.

1. *General.* The Council is pleased to report that, in 1952, the number of Fellows increased from 8616 on January 1st to 9063, the highest figure in the history of the Society, on December 31st. The net increase during the year was the largest since 1947, and was achieved in spite of the increase in the numbers lost to the Fellowship through death, resignation, or removal. Some comparative figures are given in the following table:

TABLE 1.

	1949	1950	1951	1952
Number of Fellows on January 1st	7873	8195	8353	8616
Additions:				
Elections	675	749	700	947
Reinstatements	26	29	25	34
Miscellaneous	—	1	—	1
	701	779	725	982
Deductions:				
Deaths	60	66	62	65
Resignations	210	267	273	341
Removals	109	181	127	128
Miscellaneous	—	107	—	1
	379	621	462	535
Net increase in year	322	158	263	447

As in recent years, a high proportion of the new Fellows came from overseas, especially from the United States of America. The number of Fellows participating in the Joint Subscription Scheme sponsored by the Chemical Council was 4837, an increase of 67 during the year.

2. *Honours.* The congratulations of the Society were conveyed to the following Fellows who received Honours during the year:

Knight Bachelor

Rudolph Albert Peters
Thomas Weston Johns Taylor

C.B.E.

Thomas Percy Hilditch
Frederick Measham Lea
Thomas James Drakeley
Donald Thomas Alfred Townend

The Council has also congratulated the following to whom the award of Medals was announced by the Royal Society:

Royal Medal

Professor C. K. Ingold, *President*

Davy Medal

Professor A. Robertson

3. *Deaths.* The Council deeply regrets to record the death during the year of a distinguished Past-President of the Society, Professor N. V. Sidgwick (*President* 1935—37; *Vice-President* 1925—28, 1934—35, 1937—52; *Council* 1921—24, 1928—31). The Council has also announced with regret the death of Professor Arthur Becket Lamb (Harvard), who was elected an Honorary Fellow of the Society in 1951.

III. PUBLICATIONS.

1. *Journal.* During 1952, 1046 scientific communications were received and 1000 were published. In comparison with 1951 (910 received, 788 published), these figures represent increases of 15% and 27% respectively. During 1952, 38 communications were declined, and 21 were withdrawn. Table 2 shows some comparative figures:

TABLE 2.

	1938	1948	1949	1950	1951	1952
Papers and Notes received.....	507	548	739	874	910	1046
Less rejected or withdrawn	11	17	19	68	71	59
	496	531	720	806	839	987
Papers and Notes published	404	511	870	799	778	1000
No. of pages (Papers and Notes) ...	1917 *	2203	3762	3576	3368	4901 *
No. of pages (total, excluding Index Volume)	2120 *	2330	3858	3697	3514	5056 *
Average no. of pages per communication	4·75 *	4·35	4·32	4·44	4·33	4·90 *

* Pre-war sizes of type.

The *Journal* for 1952 contained 1030 items, made up as shown in Table 3, where some comparative figures are also given. Table 4 shows that the distribution of papers between the three classes varies only slightly, but that the proportion of notes has risen steadily although it still remains fairly low.

TABLE 3.

Numbers of items in the Journal.

	1938	1948	1949	1950	1951	1952
Papers (General, Physical, and Inorganic)	102	124	147	147	131	194
,, (Physical Organic)	—	16 *	125	110	100	134
,, (Organic)	275	326	530	469	462	556
Notes	27	45	68	73	85	116
Lectures and Addresses	9	5	6	6	3	6
Obituary Notices	37	17	11	16	9	21
Annual General Meeting.....	1	2	1	1	1	2
Editorial Nomenclature Report	—	—	—	1	1	1
Report by Symbols Committee of the Royal Society	—	—	—	—	1	—
I.U.P.A.C. List of Atomic Weights	1	—	—	—	1	—
,, Report of Commission of Nomenclature of Inorganic Chemistry	—	—	—	—	1	—
	452	535	888	823	795	1030

* Class first introduced in the *Journal* for December 1948.

TABLE 4.

Percentage Distribution in the Journal.

	1938	1948	1949	1950	1951	1952
Papers (General, Physical, and Inorganic)	25·2	20·3	16·9	18·4	16·8	19·4
,, (Physical Organic)	—	3·1	14·4	13·8	12·8	13·4
,, (Organic)	74·8	63·8	60·9	58·7	59·4	55·6
Notes	6·7	8·8	7·8	9·1	10·9	11·6

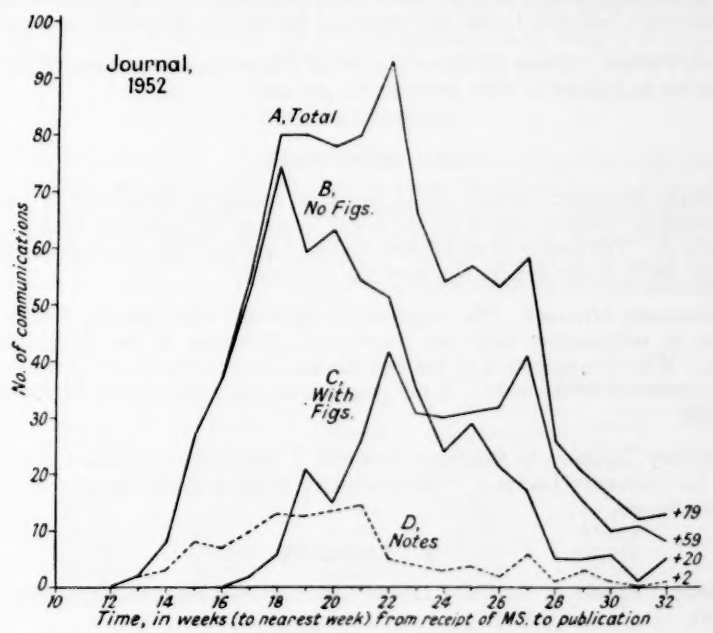
Contributions from industrial laboratories, published during 1952, totalled 90, including 5 jointly with academic institutions and 1 jointly with an industrial research organisation; during 1951 also this total was 90; expressed as a percentage of all contributions these figures are: 1952, 9·0%; 1951, 11·5%. However, contributions from Government and industrial research organisations increased both in number and proportion: 1951, 61 (7·8%); 1952, 107 (10·7%), including 14 jointly with academic institutions and 1 jointly with an industrial laboratory. The proportion from non-academic institutions remained in total about the same: 1951, 19·2%; 1952, 19·7%.

Communications from overseas, published during 1952, numbered 157, 15·7% (1951, 15·6%), including 12 jointly with British laboratories (given in parentheses in Table 5 below):

TABLE 5.

	1948	1949	1950	1951	1952
Australia	13	47	51	38(1)	62(1)
British Colonies and Protectorates	—	—	—	4(1)	6(3)
Canada	2	5	—	1	2(1)
Egypt	15	25	13	22	12
France	2	6	3	10	10
Hungary	6	2	1	1	3
India	3	3	1	3	3(1)
Irish Republic	—	6	8	5	4
Israel	2	4	6	7	10(2)
New Zealand	14	15	22	5	18
South Africa	1	10	14	10	14(1)
U.S.A.	2	10	12	13(7)	8(3)
Miscellaneous	7	8	5	2(1)	5
	67	141	136	121(10)	157(12)

The number of communications received during 1952, less the number rejected or withdrawn, was 987 (see Table 2); the number published during the year was 1000. The Figure shows the times, to the nearest week, between receipt of communications and their publication (taken as the first day of each month). Comparison of curve *B* for com-



munications without illustrations with curve *C* for those containing illustrations shows the extra four weeks required for touching up of diagrams and preparation of blocks. As a result, curve *A*, for all communications, shows a double peak. Curve *D*, for notes (these figures are included also in those shown in the other curves), shows that notes are not, in general, published faster than papers. The time taken for revision of manuscripts as a result of referees' comments discloses itself in the tailing off of the curves; but a small amount of time for discussion with referees is included in the maxima. A slight seasonal variation can be discerned in monthly figures; owing to the effect of the summer holidays on referees, printers, and authors (who take longer to return proofs and reply to referees), publication is slightly faster in the winter than in the summer. However, it is reasonable to consider that the "normal" time required for publication corresponds to the top minimum in curve *A*, *i.e.*, 20—21 weeks (4¾ months) which is ½—1 week less than in 1951, in spite of the notably greater number of publications.

2. *Annual Reports on the Progress of Chemistry for* 1951 (*Volume XLVIII*). These were issued at the end of July 1952 and contained 428 pages (490 in the previous year).

3. *Quarterly Reviews.* Volume VI (1952) contained fifteen articles, occupying 398 pages ((Volume V, eighteen articles, 423 pages).

4. *Nomenclature.* An Editorial Report on Nomenclature is being published with the index to the *Journal* for 1952. This will contain the I.U.P.A.C. rules on Organic Nomenclature (with comments by the Editor) and recent British–American agreements on the nomenclature of carbohydrates and organophosphorus (and allied) compounds. Many important changes are involved. They have been approved for use in the Society's publications and will be adopted for all MSS. submitted henceforth. Reprints will be available from the General Secretary, price 1*s.* each, post free. Reprints of the Reports for 1950 and 1951 are also available, price 1*s.* each, post free.

5. *Brochure: Presentation of Papers for the* Journal of the Chemical Society. A brochure with this title, giving instructions and advice to authors, has been issued. Each Fellow may obtain one copy gratis on application to the General Secretary, and further copies at the public price, which is 1*s.* 6*d.* per copy post free or 12*s.* 6*d.* per 10 copies post free.

6. *List of Fellows.* A new edition of the list of Fellows has been prepared, and will be made available to Fellows in 1953, price 2*s.* 6*d.* per copy.

IV. MEETINGS.

1. *Scientific Meetings.* Details of all meetings, including those held in London and those arranged at various centres by the Local Representatives of the Society, are given in Appendix A. The meetings in London included a Reception and Conversazione held on May 8th, 1952, at the Senate House of the University.

2. *Anniversary Meetings.* The Anniversary Meetings were held in Dublin on April 15th—18th in conjunction with the Anniversary Meetings of the Royal Institute of Chemistry. With the exception of the two Annual General Meetings, all the events were open to members of either body. A full programme was published in the *Proceedings* for March, 1952.

3. *Centenary Lecture.* In February Professor T. Reichstein, *Honorary Fellow* (Basle), delivered his Centenary Lecture, "The Chemistry of the Cardiac Glycosides," in London and in Manchester.

V. LIBRARY.

The Annual Report of the Joint Library Committee is reproduced as Appendix B to this Report.

VI. OTHER ACTIVITIES.

1. *"Acta Metallurgica."* The Council has agreed to become a co-operating Society in the publication of *Acta Metallurgica*, a new international journal of the science of metals. Fellows will be able to subscribe at privileged rates.

2. *Grants for Research.* The Council has authorised grants to 37 applicants amounting to £643 5*s.* 0*d.* to be made from the Research Fund.

3. *Corday-Morgan Medal and Prize.* The Corday-Morgan Medal and Prize for 1950 was awarded to Dr. R. S. Nyholm.

VII. ADMINISTRATION.

1. *Council.* At the Annual General Meeting on April 16th, the following were declared elected :

President	Professor C. K. Ingold.
Vice-Presidents who have not filled the Office of President	Professor E. L. Hirst, Sir John Simonsen.
Elected Ordinary Members of Council	Dr. D. H. R. Barton, Dr. N. Campbell, Dr. J. Chatt, Dr. S. J. Gregg, Dr. F. B. Kipping, Dr. E. A. Moelwyn-Hughes, Professor A. Robertson, Dr. M. A. T. Rogers.

Since the Annual General Meeting, Dr. S. H. Harper was co-opted under Bye-Law 42 as an Ordinary Member of Council to fill the vacancy caused by the resignation of Dr. H N. Rydon, who had ceased to reside in the area of Constituency I.

2. *Local Representatives.* The following new appointments were made to fill vacancies among the Society's Local Representatives :

Aberdeen	Dr. R. H. Thomson in place of Dr. J. M. C. Thompson.
Australia	Professor A. J. Birch in place of Dr. T. Iredale.
Edinburgh	Dr. T. R. Bolam in place of Dr. N. Campbell.
Exeter	Dr. K. Schofield in place of Dr. S. J. Gregg.
Glasgow	Dr. F. D. Gunstone in place of Dr. J. C. Speakman.
New Zealand	Professor S. N. Slater in place of Professor F. G. Soper.

VIII. FINANCE.

1. *The Cost of Publications.* The expenses of publication have risen even more sharply than in recent years and, but for the generous and much increased grants received, through the Chemical Council, from Industry, the gap between costs and income would have been very large indeed. The Society is dependent, to a much greater extent than in the past, upon outside grants to meet the expenses of its *Journal*, as well as to meet the financial requirements of the *Abstracts*. The changes in certain items of income and expenditure over the past five years are given in Table 6 below :

TABLE 6.

	Income.			*Expenditure.*		
	Annual subscriptions (net).	Sales of publications.	Outside grants.	Administration.	Journal of the Society.	Contributions to Bureau of Abstracts.
	£	£	£	£	£	£
1948	20,754	9,503	3,400	7,855	19,997	5,300
1949	22,629	13,778	5,233	7,492	31,963	5,300
1950	26,884	16,784	15,985	7,468	31,713	12,084
1951	26,928	22,358	33,500 *	7,632	36,309	14,000
1952	29,273	21,365	49,550	7,178	53,439	26,000

* Includes £9500 in respect of previous year's deficit.

2. *Contributions.* The Council wishes to express its gratitude for a contribution of £5800 received through the Royal Society from the Government Scientific Publications Grant-in-Aid and for grants totalling £43,750 received through the Chemical Council from Industry.

3. *Increased Annual Subscription.* In order to meet the steadily rising costs—especially costs of publication—the Council proposed that the rate of the Fellow's annual subscription be increased from £3 10*s.* to £4 10*s.* At the same time it was proposed that the age at which the full subscription becomes payable be raised from twenty-five to twenty-seven years of age. These proposals, with certain consequential changes in the Bye-Laws, were approved by the Fellows at an Extraordinary General Meeting held on Thursday, July 17th, 1952 (*J.*, 1952, 3663).

At the same time the schedule prices of certain publications have been increased to bring these more into line with current costs of production, and Council has decided that, in future, Fellows should be asked to certify that the publications they have ordered are for their personal use.

4. *British Abstracts.* The Society's payments to the Bureau of Abstracts have increased very rapidly in the past three years (see Table 6), and whilst these payments have been matched by correspondingly larger grants received from Industry, the ultimate financial responsibility for any deficit rests upon the Chemical Society and the Society of Chemical Industry. The two Societies are agreed that this responsibility is now too great for their financial resources, and accordingly the Bureau has been informed that the Societies must, in 1953, limit their liability to the sums originally guaranteed (£5300 in the case of the Chemical Society).

At the same time the Council has stressed the importance to British chemistry of maintaining an adequate abstract service, available to the individual at a reasonable price, and very strenuous efforts have been made which will, it is hoped, ensure that sufficient financial support is forthcoming to enable the publication of *Abstracts* to continue.

5. *Sale of Publications.* The price at which publications are sold to libraries has in some cases been increased. Libraries of Charitable Institutions will, in future, receive a discount of 10% on the price of publications ordered from the Society.

6. *Library.* The Association of British Chemical Manufacturers has agreed to continue the annual payments of £100 under Deed of Covenant to the Society for the benefit of the Library Fund for a further period of seven years. The Council has recorded its thanks to the Association.

The Council also records its thanks to the Chemical Council for a grant of £599 11*s.* 0*d.* towards the maintenance costs of the Library. Out of a total maintenance expenditure of £4717 5*s.* 4*d.* the Society has contributed from its own resources the sum of £842 0*s.* 5*d.*, as well as the entire capital expenditure for the year amounting to £2453 1*s.* 8*d.*

7. *Investments.* The following changes in the Society's Investments have been made during the year :

General Purposes Account. £1200 2½% Defence Bonds repaid at par.

£1199 7*s.* 0*d.* invested in £1000 3½% Defence Bonds and £200 3% Defence Bonds, 3rd Issue.

Special Reserve Fund. £4000 invested in £1800 3% Defence Bonds, 3rd Issue, and £2223 5*s.* 0*d.* 2½% National War Bonds, 1954/56.

Staff Pensions Fund. £2500 2½% Defence Bonds repaid at par.

£2495 17*s.* 10*d.* invested in £1000 3½% Defence Bonds, and £1505 3% Defence Bonds, 3rd Issue.

Centenary Fund. £2000 invested in £2265 16*s.* 6*d.* 4% Consolidated Stock, 1957, or after.

The Council has also approved the investment of a further £2000 in £2302 19*s.* 6*d.* 3½% Agricultural Mortgage Corporation Debenture Stock, 1975/78.

Corday-Morgan Medal and Prize Fund. £206 5*s.* 0*d.* 4½% Bristol Corporation Stock, 1952/62, repaid at par.

£206 5*s.* 0*d.* invested in £207 1*s.* 10*d.* 4¼% British Electricity Guaranteed Stock, 1974/79.

IX. REPRESENTATIVES OF THE SOCIETY ON OTHER BODIES.

In 1952 the Society was represented on various bodies by the following:

" Acta Metallurgica " :

International Journal of the Science of Metals: Dr. U. R. Evans.

Association of British Chemical Manufacturers :

Joint Technical Committee on Patents: Dr. J. T. Hewitt.

Barker Committee :

Formed to support the publication of the Barker Index of the characteristic angles of crystalline compounds: Dr. G. M. Bennett.

Bristol University Court :

Professor T. S. Moore.

British National Committee for Chemistry :

Sir Eric Rideal, Professor E. D. Hughes, Professor M. Stacey.

British National Committee for Crystallography :

Professor J. M. Robertson.

British Standards Institution. Technical Committees :

C/17.	Viscosity: Dr. A. E. Dunstan.
C/34.	Standardisation of pH Scale: Professor H. T. S. Britton.
CHE/36.	Chemicals for Electroplating: Dr. J. R. I. Hepburn.
DAC/-.	Standards for Dairying Chemistry: Mr. Eric Voelker.
FCC/HCC/1.	Nomenclature for Fine and Heavy Chemicals Industries: The Editor.
HCC/2.	Silica Gel: Dr. B. Lambert.
LBC/-.	Scientific Glassware and Related Laboratory Apparatus: Dr. G. R. Davies.
LBC/1/1.	Dean and Stark and Ubbelohde Apparatus: Dr. G. R. Davies.
LBC/5.	Hydrometers: Mr. R. Sutcliffe.
LBC/6.	Standard Distillation Apparatus: Mr. R. Sutcliffe.
LBC/11.	Microchemical Apparatus: Mr. R. Belcher, Dr. H. D. K. Drew.
LBC/11/1.	Apparatus for Microchemical Combustion Methods: Mr. R. Belcher.
LBC/11/3.	Accessory Apparatus connected with Gravimetric Microanalysis: Mr. R. Belcher.
LBC/16.	Standardization of Glass Electrodes: Dr. D. J. G. Ives.
LBC/17.	Apparatus Drawing Conventions: The Editor.
LGE/19.	Colour Terminology: Dr. F. M. Hamer.
PAC/13.	Laboratory Filter Papers: Mr. F. H. Burstall.
PCC/1.	Nomenclature for Insecticides: Professor R. L. Wain.
RUC/8.	Rubber Tubing and Bungs for Laboratory Use: Dr. L. C. Bateman.
USM/1.	Units and Technical Data: The Editor.
USM/2.	Units, Symbols and Abbreviations: The Editor.

Bureau of Abstracts :

Directors and Members : Sir Wallace Akers, Dr. G. M. Bennett, Dr. G. M. Dyson, Professor H. Burton.

Members : Mr. R. P. Bell, Dr. A. H. Cook, Professor H. N. Rydon, Professor W. Wardlaw.

Chemical Council :

The Treasurer, Mr. R. P. Bell, Professor H. Burton, Professor E. D. Hughes.

City and Guilds of London Institute :

The President.

Faraday Society. Colloidal and Biophysics Committee :

Dr. P. Johnson.

Joint Library Committee :

Dr. J. H. Burgoyne, Professor M. J. S. Dewar, Dr. F. Fairbrother, Dr. J. E. Garside, Professor E. D. Hughes, Dr. D. J. G. Ives, Professor K. Lonsdale, Professor H. N. Rydon, Dr. L. E. Sutton, Dr. F. C. Tompkins, Professor C. Tyler, Professor R. L. Wain, Dr. J. Walker, Professor W. Wardlaw.

Lawes Agricultural Trust. Committee of Management :

Sir John Simonsen.

Parliamentary and Scientific Committee :

The President, The General Secretary.

Regional Council for Further Education for the South-West. Chemistry and Chemical Technology Committee :

Professor W. E. Garner.

Royal Society : Joint Standing Committee for Symbols and Abbreviations :

Mr. R. P. Bell, The Editor.

Royal Society : Scientific Societies Accommodation Committee :

The President.

Yorkshire Council for Further Education. Advisory Committee for Chemistry in South and East Yorkshire :

Professor R. D. Haworth.

APPENDIX A.

MEETINGS HELD DURING 1952.

IN LONDON.

All meetings were held in the Rooms of the Society at Burlington House.

January 24th, The *Gustav Tamann Memorial Lecture*, by Professor W. E. Garner; February 7th, *Symposium*, "The Physical Chemistry of Structural Changes in Solids," arranged by Professor A. R. Ubbelohde. Contributions from the following were read and discussed—Professor A. R. Ubbelohde, Professor F. E. Simon, Mr. L. A. K. Staveley, Dr. J. S. Anderson, Miss H. D. Megaw, Dr. J. C. Kendrew, and Professor W. E. Garner; February 21st, *Centenary Lecture*, "The Chemistry of the Cardiac Glycosides," by Professor T. Reichstein, *Honorary Fellow*; March 13th, *Meeting* for the reading of original papers; March 27th, *Hugo Müller Lecture*, "The Chemical Exploration of the Stratosphere," by Professor F. A. Paneth; May 8th, *Meeting* for the reading of original papers; June 5th, *Meeting* for the reading of original papers; October 16th, *Tilden Lecture*, "The Stereochemistry of *cyclo*Hexane Derivatives," by Dr. D. H. R. Barton; November 6th, *Willstätter Memorial Lecture* by Sir Robert Robinson; November 20th, *Tilden Lecture*, "The Chemistry of Intermolecular Compounds," by Mr. H. M. Powell; December 4th, *Meeting* for the reading of original papers; December 18th, *Meeting* for the reading of original papers.

OUTSIDE LONDON.

Aberdeen. Joint meetings with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry, at Marischal College; January 18th, *Lecture*, "Recent Developments in Vitamin B_{12}," by Dr. T. F. Macrae; March 28th, *Lecture*, "Chromatography," by Dr. R. L. M. Synge; at Robert Gordon's Technical College, Aberdeen: October 24th, *Lecture*, "Applications of Spectroscopy to Chemical Problems," by Dr. W. C. Price; November 6th, *Lecture* by Miss Mamie Olliver; December 5th, *Lecture*, "Chemistry in Higher Technological Education," by Dr. H. J. T. Ellingham.

Australia. August 13th, a joint meeting of local Fellows and the Sydney University Chemical Society held in the Chemistry Department of the University to commemorate the birth of the late Henry George Smith. The meeting included a lecture by Professor A. J. Birch and a talk by Mr. W. J. Dunstan.

Birmingham. Joint meetings with the University Chemical Society, at the University: January 25th, *Lecture*, "Chemistry of the Tropolones," by Professor R. D. Haworth; March 14th, *Lecture*, "The Formation of Hydrogen Atoms in Aqueous Solution," by Professor F. S. Dainton; October 24th, *Lecture*, "Studies in the Chemotherapy of Tuberculosis," by Dr. V. C. Barry; December 5th, *Lecture* by Mr. B. H. Turpin (Quickfit and Quartz, Ltd.).

Bristol. At the University, January 24th, *Lecture* (with demonstration), "High Vacuum in the Service of the Chemist," by the Staff of W. Edwards and Co. (London), Ltd.; February 7th, *Lecture*, "Effect of Light on the Combustion of Hydrocarbons," by Professor R. G. W. Norrish; at the Technical College, Gloucester, February 14th, *Lecture*, "Applications of Infra-red Spectroscopy to the Study of Plastic Polymers," by Dr. H. W. Thompson. Joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry: October 1st, *Lecture*, "Synthetic Fibres," by Mr. B. T. Ridge, with the Plastics Institute at the Premier Hall, Stroud; at the University: October 2nd, *Lecture*, "Some Metallurgical Problems imposed by Stratosphere Flight," by Major P. L. Teed (with the Institute of Metals); October 30th, *Lecture*, "The Work of the Food Investigation Board," by Dr. Franklin Kidd (read by Dr. E. C. Bate-Smith); November 20th, *Lecture*, "Pile-produced Isotopes," by Dr. W. J. Arrol; November 27th, *Lecture*, "Phosphates and their Application to Industry," by Mr. C. W. Todd; December 4th, *Lecture*, "Selection of Lubricants for Industrial Applications," by Dr. Priston, at Gloucester Technical College.

Edinburgh. Joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry, at the North British Station Hotel, unless otherwise stated: January 17th, *Lecture and demonstration* by Quickfit and Quartz, Ltd.; with the Edinburgh University Chemical Society, February 5th, *Lecture,* "A Biochemical Approach to Chemotherapy," by Dr. T. S. Work, at the Biochemical Lecture Theatre, Teviot Place; February 21st, *Lecture,* "Recent Trends in Refractories Research," by Dr. A. T. Green; November 13th, *Lecture,* "Acetylenic Compounds," by Dr. R. A. Raphael.

Exeter. At the Washington Singer Laboratories, unless otherwise stated: January 22nd, *Lecture,* "Inorganic Chromatography," by Dr. F. H. Pollard, joint meeting with the Society of Chemical Industry; February 18th, *Lecture,* "Chemistry of the Tropolones," by Professor R. D. Haworth; March 13th, *Lecture,* "Some Aspects of Physical Oceanography in Antarctic and Sub-antarctic Waters," by Dr. H. F. P. Herdman, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry at the Technical College, Tavistock Road, Plymouth; May 5th, *Meeting* for the reading of original papers; October 24th, *Lecture,* "Some Unusual Applications of Surface-active Agents," by Mr. J. L. Moillett, joint meeting with the Society of Chemical Industry; October 31st, *Lecture,* "The Bacteriostatic Properties of Heterocyclic Compounds," by Dr. A. Albert; November 27th, at the Washington Singer Laboratories and November 28th, at the Technical College, Tavistock Road, Plymouth, *Lecture,* "Metallic Complex Formation and Electronic Structure," by Dr. J. Chatt.

Glasgow. January 18th, *Tilden Lecture,* "The Contributions of Wave Mechanics to Chemistry," by Professor C. A. Coulson, at the University; February 29th, Annual General Meeting of Local Fellows followed by a *Meeting* for the reading of original papers, at the University; October 24th, *Lecture,* "Substitution at an Aromatic Carbon Atom," by Professor D. H. Hey, joint meeting with the Alchemist's Club and the Andersonian Chemical Society, at the Royal Technical College; November 21st, *Lecture,* "Some Recent Work on the Chemistry of Metallic Oxides," by Dr. J. S. Anderson, at the University.

Hull. At University College: January 31st, *Lecture,* "The Physics and Chemistry of Monolayers," by Dr. J. H. Schulman; February 21st, *Lecture,* "La Liaison d'Hydrogène," by Professor L. Hunter, joint meetings with the University College Scientific Society: October 30th, *Lecture,* "Recent Progress in the Mechanism of Synthesis of High Polymers," by Professor H. W. Melville; December 11th, *Lecture,* "Chemical Research at Harwell," by Dr. R. Spence (with the Royal Institute of Chemistry).

Irish Republic. January 16th, *Lecture,* "Recent Advances in the Chemistry of Algal Polysaccharides," by Dr. F. J. Coll, at Trinity College, Dublin; March 7th, *Lecture,* "Recent Advances in Nucleotide Chemistry," by Professor A. R. Todd, joint meeting with The Werner Society at Trinity College, Dublin; April 15th to 18th, *Anniversary Meetings* held jointly with the Royal Institute of Chemistry (for full programme see *Proceedings* for March, 1952); May 16th, *Lecture,* "The Chemical Exploration of the Stratosphere," by Professor F. A. Paneth, joint meeting with the Werner Society at Trinity College, Dublin; October 22nd, *Lecture,* "Physical Chemical Methods in Sugar Industry Laboratories," by Mr. R. J. P. Carolan, joint meeting with the Institute of Chemistry of Ireland, at University College, Dublin; November 5th, *Lecture,* "Recent Physico-chemical Studies on π Electrons in Solids," by Professor A. R. Ubbelohde, at University College, Dublin; November 21st, *Lecture,* "The Molecular-orbital Theory of Organic Chemistry," by Professor M. J. S. Dewar, joint meeting with the Werner Society at Trinity College, Dublin.

Leeds. At the University: January 21st, *Royal Institute of Chemistry Lecture,* "Recent Developments in Acetylene Chemistry," by Professor E. R. H. Jones; January 29th, *Lecture,* "The New Elements," by Dr. F. Fairbrother; February 18th, *Royal Institute of Chemistry Lecture,* "Some Equilibria and Reactions of Sulphur," by Dr. G. Gee; March 4th, *Lecture,* "New Approaches to the Study of Combustion," by Professor R. G. W. Norrish, joint meeting with the University Union Chemical Society; October 28th, *Royal Institute of Chemistry Lecture,* "Detergent Action," by Professor N. K. Adam; November 25th, *Lecture,* "Chemistry of the Tropolones," by Professor R. D. Haworth. Fellows were invited to all meetings of the Royal Institute of Chemistry, Leeds Area Section, as well as to those organised by other bodies.

Liverpool. At the University, joint meetings with the Royal Institute of Chemistry, the Society of Chemical Industry, and the British Association of Chemists: January 24th, *Lecture*, "Some Recent Advances in the Chemistry and Biochemistry of Porphyrins," by Dr. A. Neuberger; March 6th, *Lecture*, "Some Aspects of the Chemistry of Group IV Elements," by Professor W. Wardlaw; November 6th, *Lecture*, "Some Aspects of the Chemistry of Sesquiterpenes," by Professor G. R. Clemo (with the University Chemical Society); November 27th, *Lecture*, "Kinetics of Halogenation of Organic Compounds," by Mr. R. P. Bell (with the University Chemical Society).

Manchester. January 17th, *Meeting* for the reading of original papers, at the College of Technology; at the University, unless otherwise stated: February 7th, *Lecture*, "Developments in the Chemistry of Macrocyclic Pigments," by Professor R. P. Linstead, joint meeting with the University Chemical Society; February 28th, *Centenary Lecture*, "The Chemistry of the Cardiac Glycosides," by Professor Dr. T. Reichstein, *Honorary Fellow*; March 27th, *Symposium* on Ion-exchange Resins, joint meeting with the Royal Institute of Chemistry, the Society of Chemical Industry, and the Institute of Petroleum; April 3rd, *Hugo Müller Lecture*, "The Chemical Exploration of the Stratosphere," by Professor F. A. Paneth; October 23rd, *Lecture*, "Derivatives of Phenols—Some Problems of Structure, Stereochemistry, and Crystal Complex Formation," by Professor Wilson Baker, joint meeting with the Royal Institute of Chemistry and Society of Chemical Industry; November 13th, *Lecture*, "Self-sustained Exothermic Chemical Reactions with Special Reference to Explosions and Jet Propulsion," by Dr. James Taylor, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, at the College of Technology; November 25th, *Meeting* for reading of original papers, at the College of Technology.

Newcastle and Durham. At King's College, Newcastle-on-Tyne, unless otherwise stated: January 25th, *Bedson Club Lecture*, "The Contributions of Wave Mechanics to Chemistry," by Professor C. A. Coulson; February 22nd, *Bedson Club Lecture*, "There and Back Again. Some Aspects of Hysteresis," by Professor D. H. Everett; March 7th, *Meeting* for the reading of original papers; May 2nd, *Bedson Club Lecture*, "Recent Advances in the Chemistry of the Heaviest Elements," by Dr. J. S. Anderson; October 24th, *Meeting* for the reading of original papers; October 30th, *Lecture*, "The Comparative Chemistry of Carbon and Silicon," by Professor E. D. Hughes, joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry at the Science Building, Durham; November 28th, *Tilden Lecture*, "The Stereochemistry of *cyclo*Hexane Derivatives," by Dr. D. H. R. Barton. Fellows were invited to the meetings of the Bedson Club.

Northern Ireland. At Queen's University, Belfast, joint meetings with the Royal Institute of Chemistry and the Society of Chemical Industry; January 30th, *Lecture*, "Recent Research on the Control of Flowering in Plants," by Dr. Eric Ashby; February 19th, *Lecture*, "On Making Jam," by Mr. E. F. Eaton; October 7th, *Lecture*, "The Winning and Utilization of Peat," by Mr. A. J. Howard. November 4th, *Lecture*, "William Higgins—His Life and Work," by Professor T. S. Wheeler; November 25th, *Lecture*, "Some Recent Advances in the Chemistry of Natural Products," by Dr. W. B. Whalley (with the Andrews Club); December 3rd, *Jubilee Memorial Lecture* of the Society of Chemical Industry, "Textile Fibres—Variations on Some Familiar Themes," by Mr. J. R. Whinfield.

North Wales. At the University College of North Wales, Bangor, joint meetings with the University College Chemical Society: January 10th, *Lecture*, "Mould Metabolic Products," by Professor Alexander Robertson; February 7th, *Lecture*, "Biological Value of Proteins," by Dr. Kathleen Henry, with the Liverpool Section of the Society of Chemical Industry; November 6th, *Lecture*, "Cortisone," by Professor C. W. Shoppee; December 4th, *Lecture*, "Some Recent Advances in the Chemistry of the Fluorine Compounds," by Professor H. J. Emeléus, with the North Wales Section of the Royal Institute of Chemistry.

Nottingham. Joint meetings with Nottingham University Chemical Society, at the University, unless otherwise stated: January 31st, *Lecture*, "The Place of the Transuranic Elements in the Periodic Table," by Dr. J. S. Anderson; February 19th, *Lecture*, "Chemistry of the Tropolones," by Professor R. D. Haworth; joint meeting with Leicester University College Chemical Society, at University College, Leicester;

March 13th, *Lecture*, "Starch Metabolism in the Higher Plants," by Professor S. Peat; October 23rd, *Lecture*, "The Molecular-orbital Theory of Organic Chemistry," by Professor M. J. S. Dewar; November 27th, *Lecture*, "Some Organometallic Compounds containing Fluorocarbon Radicals," by Professor H. J. Emeléus.

Oxford. Fellows were invited to the following Alembic Club Lectures held in the Physical Chemistry Laboratory: October 27th, *Lecture*, "Carcinogenesis," by Professor Alexander Haddow; November 10th, *Lecture*, "Herbicides and Insecticides," by Professor G. E. Blackman; November 24th, *Lecture*, "Industrial Catalysis," by Dr. D. A. Dowden.

St. Andrews and Dundee. At United College, St. Andrews, unless otherwise stated: January 11th, *Lecture*, "Isotopes in Biological Research," by Dr. G. R. Tristram, joint meeting with St. Andrews University Chemical Society; January 17th, *Lecture*, "Organic Fluorine Compounds," by Professor M. Stacey, at University College, Dundee; January 25th, *Lecture*, "New Approaches to the Study of Combustion," by Dr. G. Porter, joint meeting with St. Andrews University Chemical Society; January 31st, *Lecture*, "Some Recent Developments in Theoretical Organic Chemistry," by Professor M. J. S. Dewar, at University College, Dundee; February 1st, *Lecture*, "The Photographic Action of *X*-Rays," by Mr. A. C. Coates, joint meeting with St. Andrews University Chemical Society; February 8th, *Lecture*, "Points in Chemotherapeutic Research, by Dr. F. L. Rose, joint meeting with St. Andrews University Chemical Society; February 28th, *Lecture*, "Structural Relationships in the Hemicellulose Group," by Professor E. L. Hirst, at University College, Dundee; March 7th, *Lecture*, "Some Aspects of Aromatic Substitution," by Professor Brynmor Jones, joint meeting with St. Andrews University Chemical Society; April 11th, *Lecture*, "Mechanism of Oxidation of Organic Compounds," by Dr. W. A. Waters, joint meeting with St. Andrews University Chemical Society; April 16th, *Lecture*, "Scientific Developments in the Field of Atomic Energy," by Sir John Cockcroft, joint meeting with St. Andrews University Chemical Society; April 18th, *Lecture*, "Polyacetylenes," by Professor E. R. H. Jones, joint meeting with the Royal Institute of Chemistry; October 17th, *Lecture*, "Alchemy and Art," by Professor John Read, joint meeting with St. Andrews University Chemical Society; October 17th, *Royal Institute of Chemistry Lecture*, "Biosynthetic Pathways," by Professor J. N. Davidson, at University College, Dundee; October 23rd, *Lecture*, "Substitution Reactions at an Aromatic Carbon Atom," by Professor D. H. Hey, at University College, Dundee; October 31st, *Lecture*, "Some Organic Compounds of Sulphur of Natural Occurrence," by Professor F. Challenger, joint meeting with St. Andrews University Chemical Society; November 14th, *Lecture*, "Hairs, Muscles, and Bacterial Flagella," by Professor W. T. Astbury, joint meeting with the St. Andrews University Chemical Society; November 28th, *Royal Institute of Chemistry Lecture*, "Alchemy and Art," by Professor John Read, at University College, Dundee; December 4th, *Lecture*, "Some Recent Progress in the Synthesis of New Types of High-polymer Molecules," by Professor H. W. Melville, at University College, Dundee.

Sheffield. At the University: joint meetings with the University Chemical Society, unless otherwise stated: January 31st, *Lecture*, "Some Relations between Crystal Structures," by Dr. A. F. Wells; February 21st, *Lecture*, "Some Recent Contributions of Organic Chemistry to Medicine," by Dr. J. Walker; March 6th, *Lecture*, "The Molecular Orbital Theory of Organic Chemistry," by Professor M. J. S. Dewar; April 24th, *Lecture*, "Recent Developments in Photochemistry," by Professor R. G. W. Norrish; November 13th, *Lecture*, "Some Recent Progress in Natural Product Research," by Dr. D. H. R. Barton; November 27th, *Lecture*, "The Origin of Meteorites," by Professor F. A. Paneth, joint meeting with the Royal Institute of Chemistry.

Southampton. Joint meetings with the University Chemical Society at the University: March 7th, *Lecture*, "The Mechanism of the Breakdown of Macromolecules," by Professor H. W. Melville; March 14th, *Lecture*, "The Biochemistry of Fluoroacetate Poisoning," by Sir Rudolph Peters; May 16th, *Lecture*, "The Application of Electric Dipole Moment Measurements to Chemical Problems," by Dr. L. E. Sutton; October 24th, *Lecture*, "Atoms in Cages," by Mr. H. M. Powell; November 21st, *Lecture*, "The Nature of the Co-ordinate Link," by Dr. J. Chatt (with the Royal Institute of Chemistry); December

5th, *Lecture*, " The Transfer of Hydrogen between Organic Compounds," by Professor R. P. Linstead, joint meeting with the Portsmouth and District Chemical Society at Portsmouth Municipal College.

South Wales. At University College, Swansea, unless otherwise stated: February 6th, *Lecture*, " The Scientific Examination of Paintings," by Dr. A. E. Werner, at University College, Cardiff; March 7th, *Lecture*, " The Development of Organic Chemistry during the 20th Century," by Sir Ian Heilbron, joint meeting with University College of Swansea Chemical Society; March 14th, *Lecture*, " The Combination of Metals and Non-metals," by Dr. U. R. Evans, joint meeting with the Royal Institute of Chemistry and University College of Swansea Chemical Society; April 25th, *Lecture*, " Acetylenic Compounds," by Professor E. R. H. Jones, joint meeting with University College of Swansea Chemical Society; October 20th, *Lecture*, " Some Recent Developments in Free-radical Chemistry," by Dr. W. A. Waters, at University College, Cardiff; October 31st, *Lecture*, " Chemical Research at Harwell," by Dr. R. Spence, joint meeting with the University College of Swansea Chemical Society and the Royal Institute of Chemistry; November 17th, *Lecture*, " Some Recent Developments in the Investigation of Radical Reactions," by Professor H. W. Melville, at University College, Cardiff; November 21st, *Lecture*, " The Transfer of Hydrogen between Organic Compounds," by Professor R. P. Linstead, joint meeting with the University College of Swansea Chemical Society.

APPENDIX B.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE FOR THE YEAR 1952

During the year 1952, attendances by readers numbered 10,562, against 10,489 the previous year. The average daily attendance was thus over 36. This increase is the more striking because of the smallness of the Reading Room and the fact that it is at the top of the building and can only be reached by walking up the stairs. The number of books borrowed showed a decrease of 388, and the number of photostat pages copied (3607) was 506 fewer than in 1951. Telephone enquiries numbered 2368, a reduction of 49. During the year 378 books were added to the Library, of which 88 were presented. 716 complete volumes of periodicals were added, and 202 pamphlets. The Library now contains 53,738 volumes, of which 16,531 are books and 37,207 are complete volumes of periodicals. Arrears of binding have again been reduced, and a large number of old periodicals has been rebound.

			Additions.		
	Attendances.	Books borrowed.	Books.	Volumes of periodicals.	Pamphlets.
1952	10,562	8703 (3526 by post)	378	716	202
1951	10,489	9091 (3795 by post)	358	712	366

Practical training in special librarianship has been given to students preparing for professional examinations, and others have visited the Library to study the methods used.

Further revision and re-arrangement of books in various rooms has taken place, in order to make the best possible use of all space, and when this is completed it is proposed to present a clear statement on the position, which is one of grave difficulty.

Gifts of books, both historical and new, continue to be received, and form most welcome additions to the Library, and to all Fellows, Publishers, and others who have kindly enriched the Library in this way, the Committee tenders its grateful thanks.

THE CHEMICAL SOCIETY

INCOME AND EXPENDITURE ACCOUNTS for the Year ended 31st December, 1952.

GENERAL PURPOSES.

1951 £ s. d.	1951 £ s. d.	*Income.*	1952 £ s. d.	1952 £ s. d.
	21 6 6	Life Composition Fees		— — —
		Separate Subscriptions—		
13,114 10 4		On account of 1952	14,756 4 11	
298 18 2		On account of 1951 and previous years	242 7 7	
		Joint Subscriptions—		
12,799 12 5		On account of 1952	12,776 14 10	
81 9 8		On account of 1951 and previous years	88 10 1	
26,294 10 7			27,863 17 5	
		Deduct Amount included in last year's Income, being valuation of Arrears as per last Balance Sheet	— — —	
300 0 0				
25,994 10 7			27,863 17 5	
		Add Income Tax recovered on Subscriptions under Covenant	1409 1 11	
895 0 1		Adjustment of cost of publications supplied to Joint Members	— — —	
39 0 0				
	26,928 10 8			29,272 19 4
	862 4 6	Dividends on Investments		865 10 0
	90 18 2	Donations		95 4 9
	300 15 9	Miscellaneous Receipts		329 15 8
	£28,203 15 7			£30,563 9 9

1951 £ s. d.	1951 £ s. d.	*Expenditure.*	1952 £ s. d.	1952 £ s. d.
		Administration Expenses :		
3961 18 11		Salaries and Wages	4245 9 8	
501 9 9		Superannuation	476 10 1	
522 1 5		House Expenses, etc.	697 4 0	
168 0 0		Accountants' Charges	168 0 0	
903 11 2		Office Expenses and Stationery	813 13 8	
294 0 11		Postages	270 18 3	
723 18 4		Furniture	— — —	
557 0 5		Miscellaneous	506 13 8	
	7632 0 11			7178 9 4
	1440 4 9	Expenses of Conjoint Chemical Office ...		1305 5 1
	31 10 0	Subscriptions		36 15 0
	949 4 10	Expenses of Meetings		712 12 6
	473 7 6	Expenses of Local Representatives		480 4 1
	353 12 6	Travelling Expenses		585 7 2
		Transfers to :		
8987 5 4		Publications Account	13,636 2 10	
		Library Account :		
2334 8 9		Capital Expenditure	2453 1 8	
750 13 0		Maintenance	842 0 5	
		Special Reserve Fund :		
2200 0 0		Building and Equipment Reserve ...	— — —	
2100 0 0		Investment Reserve	— — —	
800 0 0		Staff Pensions Fund	800 0 0	
	17,172 7 1			17,751 4 11
	151 8 0	Balance, being Excess of Income over Expenditure, carried to Balance Sheet		2513 11 8
	£28,203 15 7			£30,563 9 9

Income and Expenditure Accounts for the Year ended 31st December, 1952.

PUBLICATIONS.

1951 £ s. d.	1951 £ s. d.	*Income.*	1952 £ s. d.	1952 £ s. d.
		Publication Sales (including back numbers):		
16,851 16 11		Journal and Proceedings	14,705 19 11	
2245 4 6		Annual Reports on Progress of Chemistry	2162 16 0	
1590 7 11		Quarterly Reviews	2018 16 10	
1485 2 1		Authors' Extra Reprints	2286 10 3	
		Abstracts (Back numbers only 1944 and earlier)	163 10 10	
201 1 3		Other Publications	27 9 5	
74 14 4				
	22,358 7 0			21,365 3 3
		Proceeds of Advertisements:		
1052 2 7		Journal	1193 3 1	
114 6 6		Annual Reports	187 18 0	
49 2 6		Quarterly Reviews	59 19 3	
	1215 11 7			1441 0 4
	367 14 0	Dividends on Investments		567 14 0
		Grants:		
5000 0 0		Government Publications Grant (through the Royal Society)	5800 0 0	
*19,000 0 0		The Chemical Council	43,750 0 0	
	24,000 0 0			49,550 0 0
		Donation		5 0 0
	8987 5 4	Transfer from General Purposes Account		13,656 2 10
	£56,928 17 11			£86,385 0 5

1951 £ s. d.	1951 £ s. d.	*Expenditure.*	1952 £ s. d.	1952 £ s. d.
		Expenses on account of Journal:		
4536 18 8		Salaries and Wages	4872 8 1	
388 2 1		Superannuation	445 15 3	
16,831 3 3		Printing	26,021 12 8	
6764 7 1		Paper	12,492 2 2	
3900 9 9		Banding and Distribution	4589 2 11	
2556 18 0		Authors' Reprints	3770 8 5	
62 3 6		Furniture	8 5 0	
469 13 3		Office Expenses and Stationery ...	308 0 5	
196 11 0		Postages	197 18 2	
		Travelling Expenses	152 11 8	
602 8 8		Miscellaneous	580 11 7	
	36,308 15 3			53,438 16 4
		Annual Reports on the Progress of Chemistry		3499 6 1
3240 1 6		Quarterly Reviews		3446 18 0
3380 1 2		Contribution to Bureau of Abstracts ...		†26,000 0 0
14,000 0 0				
	£56,928 17 11			£86,385 0 5

* Excluding amount received in respect of previous years taken to Special Reserve Fund.

† No provision has been made for any contribution which may be required towards meeting the deficiency of the Bureau of Abstracts. This contingent liability is estimated not to exceed £40,000.

Income and Expenditure Accounts for the Year ended 31st December, 1952.

LIBRARY.

1951 £ s. d.	1951 £ s. d.	*Income.*	1952 £ s. d.	1952 £ s. d.
		Contributions for Books, Periodicals, Binding, Fittings, and Furniture:		
2234 8 9		Transfer from General Purposes Account ...	2453 1 8	
300 0 0		Government Grant (through the Royal Society)	— — —	
	2634 8 9			2453 1 8
		Contributions towards maintenance through the Chemical Council:		
750 13 0		Chemical Society (General Purposes Account)	842 0 5	
1704 14 11		Royal Institute of Chemistry	1912 5 3	
627 17 7		Society of Chemical Industry	704 6 3	
175 7 8		Faraday Society	196 14 9	
119 5 3		Society of Public Analysts and Other Analytical Chemists	133 15 6	
129 15 8		Biochemical Society	145 11 8	
676 19 9		Chemical Council (Direct Grant)	599 11 0	
	4184 13 10			4534 4 10
		Contributions from other sources:		
100 0 0		Association of British Chemical Manufacturers	100 0 0	
50 0 0		Institute of Brewing	50 0 0	
10 10 0		Society of Dyers and Colourists	10 10 0	
36 9 3		Miscellaneous	22 10 6	
	196 19 3			183 0 6
	£7016 1 10			£7170 7 0

1951 £ s. d.	1951 £ s. d.	*Expenditure.*	1952 £ s. d.	1952 £ s. d.
		Capital Expenditure:		
1675 14 6		Books and Periodicals *	1893 2 3	
898 14 6		Binding	486 3 6	
59 19 9		Furniture	73 15 11	
	2634 8 9			2453 1 8
		Maintenance:		
3393 14 11		Salaries and Wages	3681 13 9	
310 5 0		Superannuation	329 4 0	
72 15 5		Postages	70 0 8	
273 6 2		House Expenses, etc.	312 7 9	
206 11 4		Office Expenses and Stationery	210 2 10	
125 0 3		Miscellaneous	113 16 4	
	4381 13 1			4717 5 4
	£7016 1 10			£7170 7 0

* Other than those received in exchange.

Income and Expenditure Accounts for the Year ended 31st December, 1952.

SPECIAL RESERVE FUND.

1951	*Income.*	1952	1951	*Expenditure.*	1952
£ s. d.		£ s. d.	£ s. d.		£ s. d.
106 12 0	Dividends on Investments	161 7 9			
8 16 5	Deposit Interest	25 13 4	115 8 5	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	187 1 1
£115 8 5		£187 1 1	£115 8 5		£187 1 1

SPECIAL PUBLICATIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
1829 3 4	Sales of Publications and Royalties received	2550 7 2	1353 0 5	Cost of Publications	44 10 4
69 18 2	Dividends on Investments	69 18 2	129 2 6	Miscellaneous	21 18 8
19 7 11	Deposit Interest	34 8 9			
			436 6 6	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	2588 5 1
£1918 9 5		£2654 14 1	£1918 9 5		£2654 14 1

STAFF PENSIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
800 0 0	Transfer from General Purposes Account	800 0 0	965 0 0	Pensions	965 0 0
95 14 4	Dividends on Investments	89 12 9	5 8 11	Miscellaneous	4 15 0
8 6 6	Deposit Interest	5 8 0			
66 8 1	Balance, being Excess of Expenditure over Income, carried to Balance Sheet	74 14 3			
£970 8 11		£969 15 0	£970 8 11		£969 15 0

Income and Expenditure Accounts for the Year ended 31st December, 1952.

CENTENARY FUND.

1951	*Income.*	1952	1951	*Expenditure.*	1952
£ s. d.		£ s. d.	£ s. d.		£ s. d.
555 17 6	Dividends on Investments	654 0 7	1257 16 8	Expenses of Lecturers & Delegates	166 2 2
	Balance, being Excess of Expenditure over Income, carried to Balance		30 11 10	Miscellaneous	32 14 0
732 11 0	Sheet	— — —	— — —	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	455 4 5
£1288 8 6		£654 0 7	£1288 8 6		£654 0 7

CORDAY-MORGAN MEDAL AND PRIZE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
274 15 10	Dividends on Investments	275 4 4	157 10 0	Prize	157 10 0
1 9 7	Deposit Interest	1 15 3	7 10 0	Medal	7 10 0
			30 16 6	Miscellaneous	29 16 2
			80 8 11	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	82 3 5
£276 5 5		£276 19 7	£276 5 5		£276 19 7

CORDAY-MORGAN MEMORIAL FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
433 13 6	Dividends on Investments	506 8 10	400 0 0	Grant to the Corday-Morgan Memorial Fund Executive	400 0 0
4 2 8	Deposit Interest	— — —	2 2 0	Memorial Expenses (Clause 12 of the Will)	2 14 6
			32 19 1	Miscellaneous	27 15 8
			2 15 1	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	75 18 8
£437 16 2		£506 8 10	£437 16 2		£506 8 10

Income and Expenditure Accounts for the Year ended 31st December, 1952.

FARADAY LECTURE FUND.

1951	*Income.*	1952	1951	*Expenditure.*	1952
£ s. d.		£ s. d.	£ s. d.		£ s. d.
15 8 8	Dividend on Investment	15 8 8	15 5	Miscellaneous	15 5
			14 13 3	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	14 13 3
£15 8 8		£15 8 8	£15 8 8		£15 8 8

ROBERT JOHN FLINTOFF TRUST.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
34 13 8	Dividends on Investments	34 13 8	5 5 10	Miscellaneous	1 14 8
3 3 1	Miscellaneous	— — —	32 10 11	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	32 19 0
£37 16 9		£34 13 8	£37 16 9		£34 13 8

EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
46 16 10	Dividends on Investments	46 16 10	105 0 0	Prize	— — —
	Balance, being Excess of Expenditure over Income, carried to Balance		20 0 0	Plaque	— — —
80 10 0	Sheet	— — —	2 6 10	Miscellaneous	2 6 10
			— — —	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	44 10 0
£127 6 10		£46 16 10	£127 6 10		£46 16 10

Income and Expenditure Accounts for the Year ended 31st December, 1952.

RESEARCH FUND.

1951	*Income.*	1952	1951	*Expenditure.*	1952
£ s. d.		£ s. d.	£ s. d.		£ s. d.
749 16 0	Dividends on Investments	749 16 0	779 13 0	Grants awarded	643 5 0
6 0	Deposit Interest	6 6	20 0 0	Honorarium, Longstaff Medallist	— — —
77 0 1	Grants repaid or not claimed	22 9 10	— — —	,, Hugo Müller Lecture	21 0 0
— — —	Miscellaneous	10 11 10	6 0 0	Longstaff Medal	— — —
	Balance, being Excess of Expenditure over Income, carried to Balance		40 12 7	Miscellaneous	71 6 4
19 3 6	Sheet	— — —	— — —	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	47 12 10
£846 5 7		£783 4 2	£846 5 7		£783 4 2

SPECIAL LECTURES FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
48 9 5	Dividend on Investment	50 1 10	26 5 0	Honorarium	— — —
			9 3 3	Lecture Expenses	— — —
			2 8 5	Miscellaneous	2 10 1
			10 12 9	Balance, being Excess o fIncome over Expenditure, carried to Balance Sheet	47 11 9
£48 9 5		£50 1 10	£48 9 5		£50 1 10

TILDEN LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
67 10 8	Dividends on Investments	67 10 8	47 5 0	Honoraria	31 10 0
3 3	Deposit Interest	10 6	20 15 0	Lecture Expenses	3 18 6
	Balance, being Excess of Expenditure over Income, carried to Balance		3 7 8	Miscellaneous	3 8 0
3 13 9	Sheet	— — —	— — —	Balance, being Excess of Income over Expenditure, carried to Balance Sheet	29 4 8
£71 7 8		£68 1 2	£71 7 8		£68 1 2

THE CHEMICAL SOCIETY

BALANCE SHEETS, 31st December, 1952.

GENERAL PURPOSES.

1951 £ s. d.	1951 £ s. d.	*Liabilities.*	1952 £ s. d.	1952 £ s. d.
		Sundry Creditors:		
10,968 17 0		Printing and Miscellaneous	10,993 6 2	
10,359 2 4		Fellowship Subscriptions in advance	13,628 4 3	
7468 12 6		Publications sold in advance	12,908 19 9	
13,800 0 0		Special Reserve Fund...	— — —	
700 0 0		Provision for Special Purposes	444 1 6	
	43,296 11 10			38,034 11 8
		Excess of Assets over Liabilities as per		
23,932 11 7		last Balance Sheet	24,126 12 7	
42 13 0		*Add* Life Composition Fees...	381 5 0	
23,975 4 7			24,507 17 7	
151 8 0		*Add* Excess of Income over Expenditure for year	2513 11 8	
	24,126 12 7			27,021 9 3
	£67,423 4 5			£65,056 0 11

1951 £ s. d.	*Assets.*	1952 £ s. d.
29,156 15 6	Investments as per Schedule (cost or value when acquired)	29,156 2 6
10,482 16 10	Sundry Debtors	17,785 15 5
7318 1 5	Stock of Paper (Journal, Annual Reports, and Quarterly Reviews)...	3122 7 11
20,465 10 8	Cash at Bank (including Deposit) and in hand	14,991 15 1
£67,423 4 5		£65,056 0 11

There is in addition a contingent liability estimated not to exceed £40,000 in respect of the Bureau of Abstracts.

Balance Sheets, 31st December, 1952.

PUBLICATIONS FUND.

1951	*Liabilities.*	1952	1951	*Assets.*	1952
£ s. d.		£ s. d.	£ s. d.		£ s. d.
15 11 0	Sundry Creditors	8 11 0	15 11 0	Sundry Debtors	8 11 0
10,978 19 7	Excess of Assets over Liabilities as per last Balance Sheet	10,978 19 7	10,978 19 7	Investments as per Schedule (cost or value when acquired)	10,978 19 7
£10,994 10 7		£10,987 10 7	£10,994 10 7		£10,987 10 7

SPECIAL RESERVE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.
		Publications Reserve:					
85 0 7		As per last Balance Sheet		9585 0 7	13,800 0 0	Sundry Debtors	13 3 11
9500 0 0		*Add* Grant—The Chemical Council (for 1950 and earlier years)		— — —	3,816 9 5	Investments as per Schedule (cost or value when acquired)	7,816 9 5
	9585 0 7				930 13 8	Cash at Bank and on Deposit in London Trustee Savings Bank ...	10,904 10 10
	1309 17 8	Library Reserve:					
		As per last Balance Sheet		1309 17 8			
825 0 0		Building and Equipment Reserve:					
2200 0 0		As per last Balance Sheet		3025 0 0			
	3025 0 0	*Add* Transfer General Purposes Account ...		— — —			
		Investments Reserve:					
	2100 0 0	As per last Balance Sheet		2100 0 0			
		General Purposes Reserve:					
2411 16 5		Amount brought forward	2527 4 10				
115 8 5		*Add* Excess of Income over Expenditure for year	187 1 1				
	2527 4 10			2714 5 11			
	£18,547 3 1			£18,734 4 2	£18,547 3 1		£18,734 4 2

BALANCE SHEETS, 31ST DECEMBER, 1952.

SPECIAL PUBLICATIONS FUND.

1951			*Liabilities.*	1952			1951			*Assets.*	1952		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			Sundry Creditors							Sundry Debtors			
	498	4 7			62	4 3	162	5 10			47	2 5
			Excess of Assets over Liabilities as per last Balance Sheet				2011	19 10		Investments as per Schedule (cost of value when acquired)	2011	19 10
2948	16	3		3385	2	9				Cash at Bank and on deposit in the Post Office Savings Bank and London Trustee Savings Bank			
			Add Excess of Income over Expenditure for year				1709	1 8			3976	9 10
436	6	6		2588	5	1							
	3385	2 9			5973	7 10							
	£3883	7 4			£6035	12 1	£3883	7 4			£6035	12 1	

STAFF PENSIONS FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			5	4	0	Sundry Creditors				4	15	0	Sundry Debtors			
						Excess of Assets over Liabilities as per last Balance Sheet				100	0	0		—	—	—
4122	13	9					4056	5 8		3726	6	0	Investments as per Schedule (cost or value when acquired)	3722	3	10
						Deduct Excess of Expenditure over Income for year				235	3	8	Cash at Bank and on deposit in the Post Office Savings Bank	264	2	7
66	8	1					74	14 3								
	4056	5 8					3981	11 5								
	£4061	9 8					£3986	6 5		£4061	9	8		£3986	6	5

CENTENARY FUND.

£	s.	d.	£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			27	15	10	Sundry Creditors				56	10	8	Sundry Debtors			
						Capital Account:								515	19	3
20,331	14	6				As per last Balance Sheet	22,977	11 1					Investments as per Schedule (cost or value when acquired)			
						Add Contributions under Deeds and								21,198	3	4
2,645	16	7				Donations for year	2,553	9 11					Income Account:			
	22,977	11 1					25,531	1 0		732	11	0	Excess of Expenditure over Income for year	—	—	—
						Income Account:				323	7	2	*Deduct* Accumulated Income	—	—	—
						Excess of Income over Expenditure for year	455	4 5						409	3	10
						Deduct deficit brought forward	409	3 10						882	0	6
	—	— —											Cash at Bank	2,034	15	10
	£23,005	6 11					£25,633	12 3		£23,005	6	11		£25,633	12	3

Balance Sheets, 31st December, 1952.

CORDAY–MORGAN MEDAL AND PRIZE FUND.

1951 £ s. d.	1951 £ s. d.	*Liabilities.*	1952 £ s. d.	1952 £ s. d.
	13 16 3	Sundry Creditors		13 15 2
		Capital Account :		
4985 17 9		As per last Balance Sheet	5887 10 9	
900 14 4		*Add* Received from Public Trustee	— — —	
18 8		Balance on Bonus Issue of Barclays Bank, (D.C. & O.) Ltd., "A" Stock	— — —	
— — —		Balance on Bonus Issue of Imperial Tobacco Co. (G.B. & I.) Ltd. Ordinary Stock	10 6	
5887 10 9			5888 1 3	
— — —		*Deduct* Loss on Repayment of Investment	2 11 7	
	5887 10 9			5885 9 8
		Income Account :		
1109 10 7		As per last Balance Sheet	1381 15 4	
191 15 10		*Add* Received from Public Trustee	— — —	
— — —		Income Tax recovered	43 15 1	
80 8 11		Excess of Income over Expenditure for year	82 3 5	
	1381 15 4			1507 13 10
	£7283 2 4			£7406 18 8

1951 £ s. d.	*Assets.*	1952 £ s. d.
75 0 3	Sundry Debtors	73 16 1
6860 14 9	Investments as per Schedule (cost or value when acquired)	6858 3 2
347 7 4	Cash at Bank (including Deposit)	474 19 5
£7283 2 4		£7406 18 8

CORDAY–MORGAN MEMORIAL FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
	27 9 4	Sundry Creditors		30 10 2
		Capital Account :		
8513 17 6		As per last Balance Sheet	10,090 2 8	
1576 5 2		*Add* Received from Public Trustee	— — —	
	10,090 2 8			
		Income Account:		
2204 7 5		As per last Balance Sheet	2512 19 4	
353 19 5		*Add* Received from Public Trustee	— — —	
— — —		Income Tax recovered	88 17 0	
2558 6 10			2601 16 4	
48 2 7		*Deduct* Income Tax charged on Memorial Expenses, 1950	— — —	
2510 4 3			2601 16 4	
2 15 1		*Add* Excess of Income over Expenditure for year	75 18 8	
	2512 19 4			2677 15 0
	£12,630 11 4			£12,798 7 10

£ s. d.	*Assets.*	£ s. d.
119 0 0	Sundry Debtors	120 10 0
12,232 1 5	Investments as per Schedule (cost or value when acquired)	12,232 1 5
279 9 11	Cash at Bank	445 16 5
£12,630 11 4		£12,798 7 10

BALANCE SHEETS, 31ST DECEMBER, 1952.

FARADAY LECTURE FUND.

1951 £ s. d.	£ s. d.	*Liabilities.*	1952 £ s. d.	£ s. d.	1951 £ s. d.	*Assets.*	1952 £ s. d.
	15 5	Sundry Creditors		15 5	439 4 0	Investment as per Schedule (cost or value when acquired)	439 4 0
472 16 10		Excess of Assets over Liabilities as per last Balance Sheet	487 10 1		49 1 6	Cash at Bank	63 14 9
14 13 3		*Add* Excess of Income over Expenditure for year	14 13 3				
	487 10 1			502 3 4			
	£488 5 6			£502 18 9	£488 5 6		£502 18 9

ROBERT JOHN FLINTOFF TRUST.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.
	1 17 10	Sundry Creditors		1 14 8	8 19 9	Sundry Debtors	5 2 0
1029 0 7		Excess of Assets over Liabilities as per last Balance Sheet	1045 1 6		1000 0 0	Investments as per Schedule (cost or value when acquired)	1000 0 0
16 10 0		*Deduct* Cost of die for Medals	— — —		37 19 7	Cash at Bank	74 13 2
1012 10 7			1045 1 6				
32 10 11		*Add* Excess of Income over Expenditure for year	32 19 0				
	1045 1 6			1078 0 6			
	£1046 19 4			£1079 15 2	£1046 19 4		£1079 15 2

EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.		£ s. d.
	2 6 10	Sundry Creditors		2 6 10	1101 7 11	Investments as per Schedule (cost or value when acquired)	1101 7 11
1218 5 8		Excess of Assets over Liabilities as per last Balance Sheet	1137 15 8		38 14 7	Cash at Bank	83 4 7
— — —		*Add* Excess of Income over Expenditure for year	44 10 0				
1218 5 8			1182 5 8				
80 10 0		*Deduct* Excess of Expenditure over Income for year	— — —				
	1137 15 8			1182 5 8			
	£1140 2 6			£1184 12 6	£1140 2 6		£1184 12 6

Balance Sheets, 31st December, 1952.

RESEARCH FUND.

1951 £ s. d.	*Liabilities.*	1952 £ s. d.	£ s. d.	1951 £ s. d.	*Assets.*	1952 £ s. d.
435 6 10	Sundry Creditors		793 0 4	80 14 8	Sundry Debtors	48 1 3
23,928 9 0	Excess of Assets over Liabilities as per last Balance Sheet	23,909 5 6		23,923 4 7	Investments as per Schedule (cost or value when acquired)	23,923 4 7
19 3 6	*Deduct* Excess of Expenditure over Income for year			340 13 1	Cash at Bank and on deposit in Post Office Savings Bank	778 12 10
23,909 5 6		23,909 5 6				
— — —	*Add* Excess of Income over Expenditure for year	47 12 10				
23,909 5 6			23,956 18 4			
£24,344 12 4			£24,749 18 8	£24,344 12 4		£24,749 18 8

SPECIAL LECTURES FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
	2 8 5	Sundry Creditors		2 10 1		
1644 4 1		Excess of Assets over Liabilities as per last Balance Sheet	1654 16 10			
10 12 9		*Add* Excess of Income over Expenditure for year	47 11 9			
	1654 16 10			1702 8 7		
	£1657 5 3			£1704 18 8	£1657 5 3	Investment as per Schedule (cost or value when acquired) ... ... 1615 5 0 Cash at Bank 89 13 8	£1704 18 8

TILDEN LECTURE FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
	8 1 8	Sundry Creditors		3 8 0		
1998 7 4		Excess of Assets over Liabilities as per last Balance Sheet	1994 13 7			
— — —		*Add* Excess of Income over Expenditure for year	29 4 8			
1998 7 4			2023 18 3			
3 13 9		*Deduct* Excess of Expenditure over Income for year	— — —			
	1994 13 7		2023 18 3			
	£2002 15 3		£2027 6 3	£2002 15 3		£2027 6 3

£ s. d.		£ s. d.
9 15 2	Sundry Debtors	9 15 2
1878 14 10	Investments as per Schedule (cost or value when acquired)	1878 14 10
114 5 3	Cash at Bank (including Deposit)	138 16 3

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1952.* £ s. d.
£2609 14s. 4d. 3½% Conversion Loan, 1961, or after	2044 16 0	2059 13 2
£2408 2s. 6d. 3% Funding Loan, 1959/69	2429 11 5	2095 1 4
£2400 14s. 9d. 3% Savings Bonds, 1960/70	2418 11 0	2064 12 9
£2000 3% Savings Bonds, 1965/75	2006 4 5	1680 0 0
£1000 3½% Defence Bonds	1000 0 0	1000 0 0
£200 3% Defence Bonds, 3rd Issue	199 7 0	200 0 0
£4747 4s. 5d. 3% British Transport Guaranteed Stock, 1978/88	5704 9 8	3655 7 2
£2546 1s. 4d. 3% British Electricity Guaranteed Stock, 1968/73	2549 4 5	2138 13 11
£2400 2½% Bristol Corporation Debenture Stock, 1957	2070 2 0	2184 0 0
£1550 3½% London County Consolidated Stock, 1954/59	1639 2 6	1534 10 0
£2000 3% London County Consolidated Stock, 1962/67	2032 10 0	1770 0 0
£2500 3% Commonwealth of Australia Registered Stock, 1964/66	2509 7 6	2162 10 0
£A3000 3½% Commonwealth of Australia Treasury Bonds, 1961/64	2552 16 7	2106 0 0
	£29,156 2 6	£24,650 8 4

PUBLICATIONS FUND.

£2260 19s. 9d. 3½% Conversion Loan, 1961, or after	1566 16 4	1786 3 7
£1000 3% Savings Bonds, 1955/65	1000 0 0	930 0 0
£2261 1s. 11d. 3% Savings Bonds, 1960/70	2276 1 11	1944 10 11
£2175 13s. 4d. 3% British Transport Guaranteed Stock, 1978/88	1929 1 4	1675 5 3
£2000 3% British Electricity Guaranteed Stock, 1968/73	2002 10 0	1680 0 0
£1200 3% Commonwealth of Australia Registered Stock, 1964/66	1204 10 0	1038 0 0
£982 12s. 0d. 3% Southern Rhodesia Stock, 1971/73	1000 0 0	799 16 4
	£10,978 19 7	£9853 16 1

SPECIAL RESERVE FUND.

£1165 2½% Funding Loan, 1956/61	1169 7 5	1089 5 6
£2223 5s. 0d. 2½% National War Bonds, 1954/56	2210 17 0	2195 9 2
£1800 3% Defence Bonds, 3rd Issue	1789 3 0	1800 0 0
£2582 10s. 9d. 3% Liverpool Corporation Stock, 1955/58	2647 2 0	2505 1 3
	£7816 9 5	£7589 15 11

SPECIAL PUBLICATIONS FUND.

£715 8s. 10d. 3½% Conversion Loan, 1961, or after	541 2 4	565 3 11
£746 1s. 0d. 3% British Transport Guaranteed Stock, 1978/88	719 18 9	574 9 2
£750 3% British Electricity Guaranteed Stock, 1968/73	750 18 9	630 0 0
	£2011 19 10	£1769 13 1

STAFF PENSIONS FUND.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1952.* £ s. d.
£114 1s. 11d. 3½% Conversion Loan, 1961, or after	88 2 3	90 2 10
£150 2½% National War Bonds, 1951/53	150 0 0	150 0 0
£170 3% Savings Bonds, 1955/65	170 0 0	158 2 0
£815 2s. 7d. 2½% Funding Loan, 1956/61	818 3 9	762 2 11
£1505 3% Defence Bonds, 3rd Issue	1495 17 10	1505 0 0
£1000 3½% Defence Bonds	1000 0 0	1000 0 0
	£3722 3 10	£3665 7 9

CENTENARY FUND.

£2637 10s. 6d. 3½% Conversion Loan, 1961, or after	2300 0 0	2083 12 11
£2477 13s. 11d. 3% Savings Bonds, 1955/65	2491 11 10	2304 5 2
£2500 3% Savings Bonds, 1960/70	2534 7 6	2150 0 0
£2705 18s. 7d. 2½% Savings Bonds, 1964/67	2500 0 0	2286 10 2
£2279 13s. 0d. 3% British Transport Guaranteed Stock, 1978/88	2237 7 9	1755 6 7
£2500 3% British Electricity Guaranteed Stock, 1968/73	2498 8 9	2100 0 0
£2265 16s. 6d. 4% Consolidated Stock, 1957, or after	2000 0 0	1971 5 4
£1970 1s. 0d. 3% New Zealand Stock, 1973/77	2000 0 0	1595 14 10
£1716 15s. 2d. 3½% Northern Ireland Stock, 1969/71	1700 0 0	1502 3 3
£A3500 3½% Commonwealth of Australia Treasury Bonds, 1961/64	2936 7 6	2457 0 0
	£23,198 3 4	£20,205 18 3

CORDAY-MORGAN MEDAL AND PRIZE FUND.

£1398 5s. 4d. 3½% War Stock, 1952, or after	1325 14 0	1090 13 0
£635 3s. 10d. 3% British Transport Guaranteed Stock, 1978/88	574 17 0	489 1 11
£207 1s. 10d. 4½% British Electricity Guaranteed Stock, 1974/79	206 5 0	207 1 10
£206 5s. 0d. 4% Consolidated Stock, 1957, or after	213 9 4	179 8 9
£137 10s. 0d. 3½% Bournemouth Corporation Stock Red., 1958/62	133 14 5	129 18 9
£206 8s. 0d. 4½% Hertfordshire County Council Stock, 1955/65	215 0 4	208 6 3
£300 3½% Hertfordshire County Council Stock, 1954/59	297 15 0	297 0 0
£774 6s. 2d. 3% British Guiana Government Stock, 1975/80	699 5 4	600 1 10
£137 10s. 0d. 3% Federated Malay States Government Stock, 1960/70	120 6 3	109 6 3
£112 Barclays Bank (D. C. & O.) Ltd., "A" Ordinary £1 Stock Units	201 7 6	196 0 0
£172 Mitchells & Butlers, Ltd., Ordinary £1 Stock Units	713 16 0	473 0 0
£206 Watney, Combe & Reid, Ltd., Deferred Ordinary £1 Shares	597 8 0	566 10 0
£83 Imperial Tobacco Co. (G.B. & I.) Ltd., Ordinary £1 Shares	263 5 0	237 11 9
£240 Cardinal Investment Trust, Ltd., 3½% Convertible Debenture Stock	291 0 0	296 8 0
£104 Commercial Union Assurance Co., Ltd., Ordinary £1 Stock Units	1014 0 0	1079 0 0
	£6838 3 2	£6159 8 4

SCHEDULE OF INVESTMENTS.

CORDAY-MORGAN MEMORIAL FUND.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December, 1952.*
	£ s. d.	£ s. d.
£1530 2s. 5d. 3½% Conversion Loan, 1961, or after	1426 4 2	1208 15 11
£1973 16s. 11d. 3½% War Stock, 1952, or after	1880 1 10	1539 12 0
£477 1s. 10d. 3% British Electricity Guaranteed Stock, 1968/73 ...	450 17 0	400 15 1
£1062 10s. 11d. 3% British Gas Guaranteed Stock, 1990/95	894 5 7	818 3 2
£217 12s. 6d. 3% London County Consolidated Stock, 1962/67 ...	208 7 6	191 14 3
£1035 0s. 7d. 3% Redemption Stock, 1986/96	928 18 10	802 2 11
£1000 4% South Staffordshire Waterworks Red. Preference Stock, 1971	1046 10 6	895 0 0
£300 4½% Hull Corporation Stock, 1952/72	303 15 0	300 0 0
£412 10s. 0d. 3% City of Plymouth Stock, 1954	405 5 7	410 8 9
£137 10s. 0d. 4½% Kenya Government Stock, 1961/71	148 16 11	136 16 3
£300 3% New Zealand Government Stock, 1952/55	298 10 0	298 10 0
£68 Barclays Bank, Ltd., "B" Ordinary £1 Stock Units	237 3 0	197 4 0
£206 Benskins Watford Brewery, Ltd., Ordinary £1 Shares	684 19 0	669 10 0
£206 H. & G. Simmonds, Ltd., Ordinary £1 Stock Units	824 0 0	592 5 0
£160 Imperial Tobacco (G.B. & I.) Ltd., Ordinary £1 Shares	506 5 0	458 0 0
£108 Thomas Tilling & Co., Ltd., Ordinary £1 Stock Units	107 6 6	126 18 0
£340 Alliance Trust, Ltd., 4½% Debenture Stock, 1956	344 5 0	311 2 0
£69 London & Lancashire Insurance Co., Ltd., Ordinary £1 Stock Units	448 10 9	457 2 6
£68 Phœnix Assurance Co., Ltd., Ordinary £1 Stock Units	1088 0 0	1156 0 0
	£12,232 1 5	£10,969 19 10

FARADAY LECTURE FUND.

£441 1s. 11d. 3½% Conversion Loan, 1961, or after	£439 4 0	£348 9 4

ROBERT JOHN FLINTOFF TRUST.

£523 2s. 2d. 3½% Conversion Loan, 1961, or after	500 0 0	413 5 1
£545 19s. 4d. 3% British Transport Guaranteed Stock, 1978/88 ...	500 0 0	420 7 11
	£1000 0 0	£833 13 0

EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

Nominal Details.	*Cost or Value when Acquired.*	*Market Value 31st December, 1952.*
	£ s. d.	£ s. d.
£61 15s. 8d. 3½% Conversion Loan, 1961, or after	50 1 5	48 16 2
£1489 10s. 6d. 3% British Transport Guaranteed Stock, 1978/88 ...	1051 6 6	1146 18 8
	£1101 7 11	£1195 14 10

RESEARCH FUND.

£4177 16s. 1d. 3½% Conversion Loan, 1961, or after	3625 16 8	3300 9 4
£500 3% Defence Bonds, 4th issue	500 0 0	500 0 0
£1835 2½% Funding Loan, 1956/61	1835 0 0	1715 14 6
£1500 3% Savings Bonds, 1955/65	1515 0 0	1395 0 0
£4000 3% Savings Bonds, 1960/70	4060 0 0	3440 0 0
£3755 2s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	3567 19 5	2891 8 7
£3719 8s. 2d. 3% British Electricity Guaranteed Stock, 1968/73 ...	3724 1 2	3124 6 1
£4000 3% Commonwealth of Australia Registered Stock, 1964/66 ...	4015 0 0	3460 0 0
£1116 7s. 0d. 3% New Zealand Stock, 1973/77	1080 7 4	904 4 10
	£23,923 4 7	£20,731 3 4

SPECIAL LECTURES FUND

£1069 17s. 3d. 3% British Transport Guaranteed Stock, 1978/88 ...	£1615 5 0	£1285 15 10

TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Loan, 1959/69	386 12 10	364 14 10
£681 19s. 1d. 3% British Transport Guaranteed Stock, 1978/88 ...	625 2 0	525 2 1
186 National Provincial Bank Shares £5 each, £1 paid "B"	678 18 0	548 14 0
£220 3% Metropolitan Water Board (Kent Water Works) Deb. Stock	188 2 0	148 10 0
	£1878 14 10	£1587 0 11

W. A. AKERS, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith and, in our opinion, correct. We have also verified the Balances at the Bankers and Investments.

FINSBURY CIRCUS HOUSE,
BLOMFIELD STREET, E.C.2.
19th MARCH, 1953.

W. B. KEEN & CO.
Chartered Accountants.

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